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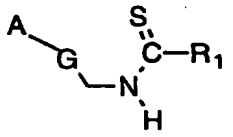
(54) Title: OXAZOLIDINONE ANTIBACTERIAL AGENTS HAVING A THIOCARBONYL FUNCTIONALITY



(I)

(57) Abstract

The present invention provides compounds of Formula (I) or pharmaceutical acceptable salts thereof wherein A, G and R_1 are as defined in the claims which are antibacterial agents.

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OXAZOLIDINONE ANTIBACTERIAL AGENTS HAVING A THIOCARBONYL FUNCTIONALITY

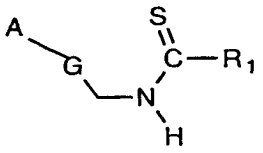
BACKGROUND OF THE INVENTION

The present invention relates to new and useful oxazolidinone compounds and their preparations, and more particularly to oxazolidinone compounds in which the carbonyl functionality of -NH-C(O)-R is converted to a thiocarbonyl functionality, such as a thiourea -NH-C(S)-NH_2, an alkyl thiourea -NH-C(S)-NH-(C_{1-4} alkyl), thioamide -NH-C(S)-(C_{1-4} alkyl) or -NH-C(S)-H.

Replacement of the oxygen atom with a sulfur atom has unexpectedly improved the antimicrobial properties of the compounds. The compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens, including Gram-positive aerobic bacteria such as multiply-resistant staphylococci and streptococci, Gram-negative organisms such as H. *influenzae* and M. *catarrahlis* as well as anaerobic organisms such as bacteroides and clostridia species, and acid-fast organisms such as *Mycobacterium tuberculosis* and *Mycobacterium avium*. The compounds are particularly useful because they are effective against the latter organisms which are known to be responsible for infection in persons with AIDS.

SUMMARY OF THE INVENTION

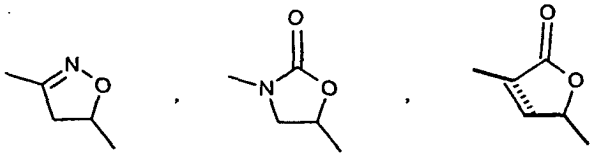
In one aspect the subject invention is a compound of the Formula I



I

or pharmaceutical acceptable salts thereof wherein:

G is



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R_1 is

a) H,

b) NH_2,

c) NH-C_{1-4} alkyl,

d) C_{1-4} alkyl,

e) -OC_{1-4} alkyl,

f) -S C_{1-4} alkyl,

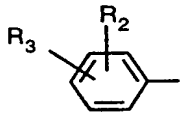
g) C_{1-4} alkyl substituted with 1-3 F, 1-2 Cl, CN or -COOC_{1-4} alkyl,

h) C_{3-6} cycloalkyl,

i) N(C_{1-4} alkyl)$_2$ or

j) $N(CH_2)_{2-5}$;

A is

a) 

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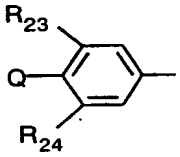
b) 

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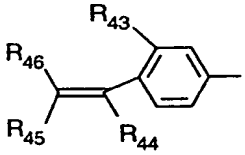
c) 

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d) a 5-membered heteroaromatic moiety having one to three atoms selected from the group consisting of S, N, and O,

wherein the 5-membered heteroaromatic moiety is bonded via a carbon atom,

wherein the 5-membered heteroaromatic moiety can additionally have a fused-on benzene or naphthyl ring,

wherein the heteroaromatic moiety is optionally substituted with one to three R_{48},

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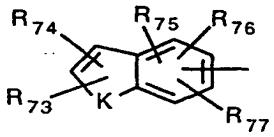
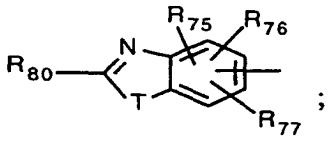
e) a 6-membered heteroaromatic moiety having at least one nitrogen atom,
wherein the heteroaromatic moiety is bonded via a carbon atom,
wherein the 6-membered heteroaromatic moiety can additionally have a fused-on benzene or naphthyl ring,
wherein the heteroaromatic moiety is optionally substituted with one to three R_{55},

f) a β-carbolin-3-yl, or indolizinyl bonded via the 6-membered ring, optionally substituted with one to three R_{55},

g)  , or

h)  ;

wherein R_2 is

a) H,
b) F,
c) Cl,
d) Br,
e) C_{1-3} alkyl,
f) NO_2, or
g) R_2 and R_3 taken together are -O-$(CH_2)_h$-O-;

R_3 is

a) -S(=O)$_i$ R_4,
b) -S(=O)$_2$-N=S(O)$_j$$R_5$$R_6$,
c) -SC(=O)R_7,
d) -C(=O)R_8,
e) -C(=O)R_9,
f) -C(=O)N$R_{10}$$R_{11}$,

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g) $-C(=NR_{12})R_8$,
h) $-C(R_8)(R_{11})-OR_{13}$,
i) $-C(R_9)(R_{11})-OR_{13}$,
j) $-C(R_8)(R_{11})-OC(=O)R_{13}$,
k) $-C(R_9)(R_{11})-OC(=O)R_{13}$,
l) $-NR_{10}R_{11}$,
m) $-N(R_{10})-C(=O)R_7$,
n) $-N(R_{10})-S(=O)_iR_7$,
o) $-C(OR_{14})(OR_{15})R_8$,
p) $-C(R_8)(R_{16})-NR_{10}R_{11}$, or
q) C_{1-8} alkyl substituted with one or more =O other than at alpha position, $-S(=O)_iR_{17}$, $-NR_{10}R_{11}$, C_{2-5} alkenyl, or C_{2-5} alkynyl;

R_4 is

a) C_{1-4} alkyl optionally substituted with one or more halos, OH, CN, $NR_{10}R_{11}$, or $-CO_2R_{13}$,
b) C_{2-4} alkenyl,
c) $-NR_{16}R_{18}$,
d) $-N_3$,
e) $-NHC(=O)R_7$,
f) $-NR_{20}C(=O)R_7$,
g) $-N(R_{19})_2$,
h) $-NR_{16}R_{19}$, or
i) $-NR_{19}R_{20}$,

R_5 and R_6 at each occurrence are the same or different and are

a) C_{1-2} alkyl, or
b) R_5 and R_6 taken together are $-(CH_2)_k-$;

R_7 is C_{1-4} alkyl optionally substituted with one or more halos;

R_8 is

a) H, or
b) C_{1-8} alkyl optionally substituted with one or more halos, or C_{3-8} cycloalkyl;

R_9 is C_{1-4} alkyl substituted with one or more

a) $-S(=O)R_{17}$,
b) $-OR_{13}$,
c) $-OC(=O)R_{13}$,
d) $-NR_{10}R_{11}$, or

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e) C_{1-5} alkenyl optionally substituted with CHO;

R_{10} and R_{11} at each occurrence are the same or different and are

a) H,

b) C_{1-4} alkyl, or

c) C_{3-8} cycloalkyl;

R_{12} is

a) $-NR_{10}R_{11}$,

b) $-OR_{10}$; or

c) $-NHC(=O)R_{10}$;

R_{13} is

a) H, or

b) C_{1-4} alkyl;

R_{14} and R_{15} at each occurrence are the same or different and are

a) C_{1-4} alkyl, or

b) R_{14} and R_{15} taken together are $-(CH)_l-$;

R_{16} is

a) H,

b) C_{1-4} alkyl, or

c) C_{3-8} cycloalkyl;

R_{17} is

a) C_{1-4} alkyl, or

b) C_{3-8} cycloalkyl;

R_{18} is

a) H,

b) C_{1-4} alkyl,

c) C_{2-4} alkenyl,

d) C_{3-4} cycloalkyl,

e) $-OR_{13}$ or

f) $-NR_{21}R_{22}$;

R_{19} is

a) Cl,

b) Br, or

c) I;

R_{20} is a physiologically acceptable cation;

R_{21} and R_{22} at each occurrence are the same or different and are

a) H,

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b) C_{1-4} alkyl, or

c) $-NR_{21}R_{22}$ taken together are $-(CH_2)_m-$;

wherein R_{23} and R_{24} at each occurrence are the same or different and are

a) H,

b) F,

c) Cl,

d) C_{1-2} alkyl,

e) CN

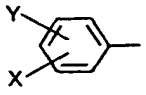
f) OH,

g) C_{1-2} alkoxy,

h) nitro, or

i) amino;

Q is

a) 

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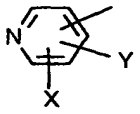
b) 

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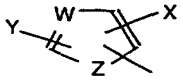
c) 

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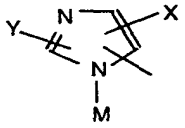
d) 

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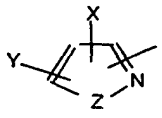
e) 

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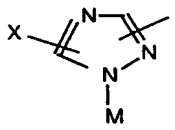
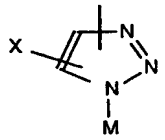
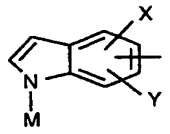
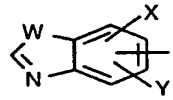
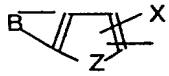
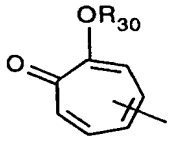
f)  ,

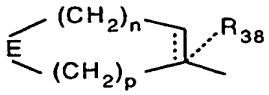
g)  ,

h)  ,

i)  ,

j) 

k)  ,

l)  ,

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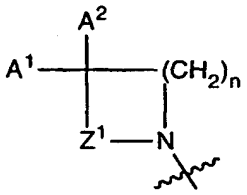
m) a diazinyl group optionally substituted with X and Y,

n) a triazinyl group optionally substituted with X and Y,

o) a quinolinyl group optionally substituted with X and Y,

p) a quinoxalinyl group optionally substituted with X and Y,

q) a naphthyridinyl group optionally substituted with X and Y,

r) 

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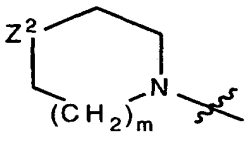
s) 

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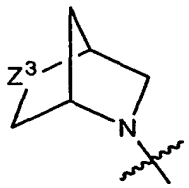
t) 

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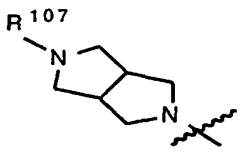
u) 

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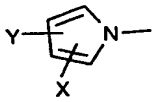
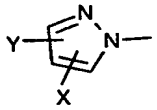
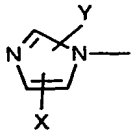
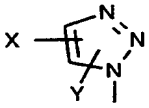
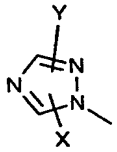
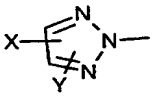
v)  ,

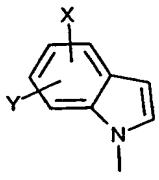
w)  ,

x)  ,

y)  ,

z)  ,

aa)  ,

bb)  or,

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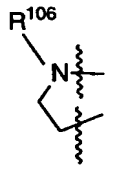
Q and R_{24} taken together are



wherein Z^1 is

a) $-CH_2-$,
b) $-CH(R^{104})-CH_2-$,
c) -C(O)-, or
d) $-CH_2CH_2CH_2-$;

wherein Z^2 is

a) $-O_2S-$,
b) -O-,
c) $-N(R^{107})-$,
d) -OS-, or
e) -S-;

wherein Z^3 is

a) $-O_2S-$,
b) -O-,
c) -OS-, or
d) -S-;

wherein A^1 is

a) H-, or
b) CH_3;

wherein A^2 is

a) H-,
b) HO-,
c) CH_3-,
d) CH_3O-,
e) $R^{102}O-CH_2-C(O)-NH-$
f) $R^{103}O-C(O)-NH-$,
g) (C_1-C_2)alkyl-O-C(O)-,
h) $HO-CH_2-$,
i) CH_3O-NH-,
j) (C_1-C_3)alkyl-O_2C-

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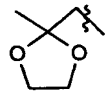
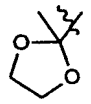
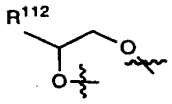
k) CH_3-C(O)-,

l) CH_3-C(O)-CH_2-,

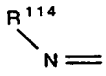
m)  , or

n)  ,

A^1 and A^2 taken together are:

a)  ,

b) O= , or

c)  ;

wherein R^{102} is

a) H-,

b) CH_3-,

c) phenyl-CH_2-, or

d) $CH_3C(O)$-;

wherein R^{103} is

a) (C_1-C_3)alkyl-, or

b) phenyl-;

wherein R^{104} is

a) H-, or

b) HO-;

wherein R^{105} is

a) H-,

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b) $(C_1\text{-}C_3)$alkyl-,

c) $CH_2 = CH\text{-}CH_2$-, or

d) $CH_3\text{-}O\text{-}(CH_2)_2$-;

wherein R^{106} is

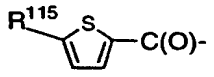
a) $CH_3\text{-}C(O)$-,

b) H-C(O)-,

c) $Cl_2CH\text{-}C(O)$-,

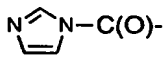
d) $HOCH_2\text{-}C(O)$-,

e) CH_3SO_2-,

f) 

,

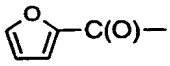
g) $F_2CHC(O)$-,

h) 

,

i) $H_3C\text{-}C(O)\text{-}O\text{-}CH_2\text{-}C(O)$-,

j) $H\text{-}C(O)\text{-}O\text{-}CH_2\text{-}C(O)$-,

k) 

,

l) $HC\equiv C\text{-}CH_2O\text{-}CH_2\text{-}C(O)$-, or

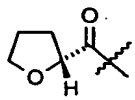
m) phenyl-$CH_2\text{-}O\text{-}CH_2\text{-}C(O)$-;

wherein R^{107} is

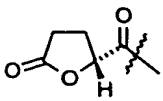
a) $R^{102}O\text{-}C(R^{110})(R^{111})\text{-}C(O)$-,

b) $R^{103}O\text{-}C(O)$-,

c) $R^{108}\text{-}C(O)$-,

d) 

,

e) 

,

f) $H_3C\text{-}C(O)\text{-}(CH_2)_2\text{-}C(O)$-,

g) $R^{109}\text{-}SO_2$-,

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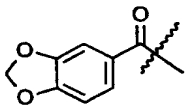
h)  ,

i) $HO\text{-}CH_2\text{-}C(O)\text{-}$,

j) $R^{116}\text{-}(CH_2)_2\text{-}$,

k) $R^{113}\text{-}C(O)\text{-}O\text{-}CH_2\text{-}C(O)\text{-}$,

l) $(CH_3)_2N\text{-}CH_2\text{-}C(O)\text{-}NH\text{-}$,

m) $NC\text{-}CH_2\text{-}$, or

n) $F_2\text{-}CH\text{-}CH_2\text{-}$;

wherein R^{108} is

a) H-,

b) $(C_1\text{-}C_4)$alkyl,

c) aryl $\text{-}(CH_2)_p$,

d) $ClH_2C\text{-}$,

e) $Cl_2HC\text{-}$,

f) $FH_2C\text{-}$,

g) $F_2HC\text{-}$, or

h) $(C_3\text{-}C_6)$cycloalkyl;

wherein R^{109} is

a) $\text{-}CH_3$,

b) $\text{-}CH_2Cl$

c) $\text{-}CH_2CH{=}CH_2$,

d) aryl, or

e) $\text{-}CH_2CN$;

wherein R^{110} and R^{111} are independently

a) H-,

b) $CH_3\text{-}$; or

wherein R^{112} is

a) H-,

b) $CH_3O\text{-}CH_2O\text{-}CH_2\text{-}$, or

c) $HOCH_2\text{-}$;

wherein R^{113} is

a) $CH_3\text{-}$,

b) $HOCH_2\text{-}$,

c) $(CH_3)_2N$-phenyl, or

d) $(CH_3)_2N\text{-}CH_2\text{-}$;

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wherein R^{114} is

a) HO-,

b) CH_3O-,

c) H_2N-,

d) CH_3O-C(O)-O-,

e) CH_3-C(O)-O-CH_2-C(O)-O-,

f) phenyl-CH_2-O-CH_2-C(O)-O-,

g) HO-$(CH_2)_2$-O-,

h) CH_3O-CH_2-O-$(CH_2)_2$-O-, or

i) CH_3O-CH_2-O-;wherein R^{113} is

a) CH_3-,

b) $HOCH_2$-,

c) $(CH_3)_2N$-phenyl, or

d) $(CH_3)_2N$-CH_2-;

wherein R^{115} is

a) H-, or

b) Cl-;

wherein R^{116} is

a) HO-

b) CH_3O-, or

c) F;

B is an unsaturated 4-atom linker having one nitrogen and three carbons;

M is

a) H,

b) C_{1-8} alkyl,

c) C_{3-8} cycloalkyl,

d) -$(CH_2)_m$$OR_{13}$, or

e) -$(CH_2)_h$-$NR_{21}R_{22}$;

Z is

a) O,

b) S, or

c) NM;

W is

a) CH,

b) N, or

c) S or O when Z is NM;

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Y is

a) H,
b) F,
c) Cl,
d) Br,
e) C_{1-3} alkyl, or
f) NO_2;

X is

a) H,
b) -CN,
c) OR_{27},
d) halo,
e) NO_2,
f) tetrazoyl,
g) -SH,
h) $-S(=O)_iR_4$,
i) $-S(=O)_2-N=S(O)_jR_5R_6$,
j) $-SC(=O)R_7$,
k) $-C(=O)R_{25}$,
l) $-C(=O)NR_{27}R_{28}$,
m) $-C(=NR_{29})R_{25}$,
n) $-C(R_{25})(R_{28})-OR_{13}$,
o) $-C(R_{25})(R_{28})-OC(=O)R_{13}$,
p) $-C(R_{28})(OR_{13})-(CH_2)_h-NR_{27}R_{28}$,
q) $-NR_{27}R_{28}$,
r) $-N(R_{27})C(=O)R_7$,
s) $-N(R_{27})-S(=O)_iR_7$,
t) $-C(OR_{14})(OR_{15})R_{28}$,
u) $-C(R_{25})(R_{16})-NR_{27}R_{26}$, or
v) C_{1-8} alkyl substituted with one or more halos, OH, =O other than at alpha position, $-S(=O)_iR_{17}$, $-NR_{27}R_{28}$, C_{2-5} alkenyl, C_{2-5} alkynyl, or C_{3-8} cycloalkyl;

R_4, R_5, R_6, R_7, R_{13}, R_{14}, R_{15}, R_{16}, and R_{17} are the same as defined above;

R_{25} is

a) H,
b) C_{1-8} alkyl optionally substituted with one or more halos, C_{3-8}

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cycloalkyl, C_{1-4} alkyl substituted with one or more of $-S(=O)_iR_{17}$, $-OR_{13}$, or $OC(=O)R_{13}$, $NR_{27}R_{28}$, or

c) C_{2-5} alkenyl optionally substituted with CHO, or CO_2R_{13};

R_{26} is

a) R_{28}, or

b) $NR_{27}N_{28}$;

R_{27} and R_{28} at each occurrence are the same or different and are

a) H,

b) C_{1-8} alkyl,

c) C_{3-8} cycloalkyl,

d) $-(CH_2)_mOR_{13}$,

e) $-(CH_2)_h-NR_{21}R_{22}$, or

f) R_{27} and R_{28} taken together are $-(CH_2)_2O(CH_2)_2-$, $-(CH_2)_hCH(COR_7)-$, or $-(CH_2)_2N(CH_2)_2(R_7)$;

R_{29} is

a) $-NR_{27}R_{28}$,

b) $-OR_{27}$, or

c) $-NHC(=O)R_{28}$;

wherein R_{30} is

a) H,

b) C_{1-8} alkyl optionally substituted with one or more halos, or

c) C_{1-8} alkyl optionally substituted with one or more OH, or C_{1-6} alkoxy;

wherein E is

a) NR_{39},

b) $-S(=O)_i$, or

c) O;

R_{38} is

a) H,

b) C_{1-6} alkyl,

c) $-(CH_2)_q$-aryl, or

d) halo;

R_{39} is

a) H,

b) C_{1-6} alkyl optionally substituted with one or more OH, halo, or -CN,

c) $-(CH_2)_q$-aryl,

d) $-CO_2R_{40}$,

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e) $-COR_{41}$,

f) $-C(=O)-(CH_2)_q-C(=O)R_{40}$,

g) $-S(=O)_2-C_{1-6}$ alkyl,

h) $-S(=O)_2-(CH_2)_q$-aryl, or

i) $-(C=O)_j$-Het;

R_{40} is

a) H,

b) C_{1-6} alkyl optionally substituted with one or more OH, halo, or -CN,

c) $-(CH_2)_q$-aryl, or

d) $-(CH_2)_q-OR_{42}$;

R_{41} is

a) C_{1-6} alkyl optionally substituted with one or more OH, halo, or -CN,

b) $-(CH_2)_q$-aryl, or

c) $-(CH_2)_q-OR_{42}$;

R_{42} is

a) H,

b) C_{1-6} alkyl,

c) $-(CH_2)_q$-aryl, or

d) $-C(=O)-C_{1-6}$ alkyl;

aryl is

a) phenyl,

b) pyridyl, or

c) napthyl; a to c optionally substituted with one or more halo, -CN, OH, SH, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} alkylthio;

wherein R_{43} is

a) H,

b) C_{1-2} alkyl,

c) F, or

d) OH;

R_{44} is

a) H,

b) CF_3,

c) C_{1-3} alkyl optionally substituted with one or more halo,

d) phenyl optionally substituted with one or more halo,

e) R_{44} and R_{45} taken together are a 5-, 6-, or 7-membered ring of the

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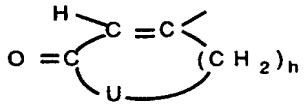
formula,

or 

f) R_{44} and R_{45} taken together are $-(CH_2)_k-$, when R_{46} is an electron-withdrawing group;

R_{45} and R_{46} at each occurrence are the same or different and are

a) an electron-withdrawing group,

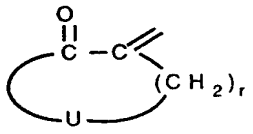
b) H,

c) CF_3,

d) C_{1-3} alkyl optionally substituted with one halo,

e) phenyl, provided at least one of R_{45} or R_{46} is an electron-withdrawing group, or

f) R_{45} and R_{46} taken together are a 5-, 6-, 7-membered ring of the formula

 ;

U is

a) CH_2,

b) O,

c) S, or

d) NR_{47};

R_{47} is

a) H, or

b) C_{1-5} alkyl;

wherein R_{48} is

a) carboxyl,

b) halo,

c) -CN,

d) mercapto,

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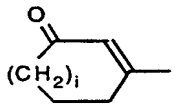
e) formyl,
f) CF_3,
g) $-NO_2$,
h) C_{1-6} alkoxy,
i) C_{1-6} alkoxycarbonyl,
j) C_{1-6} alkythio,
k) C_{1-6} acyl,
l) $-NR_{49}R_{50}$,
m) C_{1-6} alkyl optionally substituted with OH, C_{1-5} alkoxy, C_{1-5} acyl, or $-NR_{49}R_{50}$,
n) C_{2-8} alkenylphenyl optionally substituted with one or two R_{51},
o) phenyl optionally substituted with one or two R_{51},
p) a 5-, or 6-membered (un)saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with one or two R_{51}, or
q)  ;

R_{49} and R_{50} at each occurrence are the same or different and are
a) H,
b) C_{1-4} alkyl,
c) C_{5-6} cycloalkyl, or
d) R_{49} and R_{50} taken together with the nitrogen atom is a 5-, 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, and O, and can in turn be optionally substituted with, including on the further nitrogen atom, C_{1-3} alkyl, or C_{1-3} acyl;

R_{51} is
a) carboxyl,
b) halo,
c) -CN,
d) mercapto,
e) formyl,
f) CF_3,
g) $-NO_2$,
h) C_{1-6} alkoxy,

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i) C_{1-6} alkoxycarbonyl,
j) C_{1-6} alkythio,
k) C_{1-6} acyl,
l) C_{1-6} alkyl optionally substituted with OH, C_{1-5} alkoxy, C_{1-5} acyl, or $-NR_{49}R_{50}$,
m) phenyl,
n) $-C(=O)NR_{52}R_{53}$,
o) $-NR_{49}R_{50}$,
p) $-N(R_{52})(-SO_2R_{54})$,
q) $-SO_2-NR_{52}R_{53}$, or
r) $-S(=O)_iR_{54}$;

R_{52} and R_{53} at each occurrence are the same or different and are
a) H,
b) C_{1-6} alkyl, or
c) phenyl;

R_{54} is
a) C_{1-4} alkyl, or
b) phenyl optionally substituted with C_{1-4} alkyl;

wherein R_{55} is
a) carboxyl,
b) halo,
c) -CN,
d) mercapto,
e) formyl,
f) CF_3,
g) $-NO_2$,
h) C_{1-6} alkoxy,
i) C_{1-6} alkoxycarbonyl,
j) C_{1-6} alkythio
k) C_{1-6} acyl,
l) $-NR_{56}R_{57}$,
m) C_{1-6} alkyl optionally substituted with OH, C_{1-5} alkoxy, C_{1-5} acyl, or $-NR_{56}R_{57}$,
n) C_{2-8} alkenylphenyl optionally substituted with one or two R_{58},
o) phenyl optionally substituted with one or two R_{58},
p) a 5- or 6-membered (un)saturated heterocyclic moiety having one to

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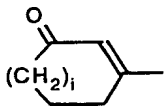
three atoms selected from the group consisting of S, N, and O, optionally substituted with one or two R_{58}, or

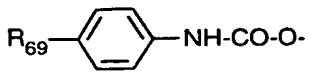
q)  ;

R_{56} and R_{57} at each occurrence are the same or different and are

a) H,
b) formyl,
c) C_{1-4} alkyl,
d) C_{1-4} acyl,
e) phenyl,
f) C_{3-6} cycloalkyl, or
g) R_{56} and R_{57} taken together with the nitrogen atom is a 5-, 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, and O, and can in turn be optionally substituted with, including on the further nitrogen atom, phenyl, pyrimidyl, C_{1-3} alkyl, or C_{1-3} acyl;

R_{58} is

a) carboxyl,
b) halo,
c) -CN,
d) mercapto,
e) formyl,
f) CF_3,
g) $-NO_2$,
h) C_{1-6} alkoxy,
i) C_{1-6} alkoxycarbonyl,
j) C_{1-6} alkythio,
k) C_{1-6} acyl,
l) phenyl,
m) C_{1-6} alkyl optionally substituted with OH, azido, C_{1-5} alkoxy, C_{1-5} acyl, $-NR_{65}R_{66}$, $-SR_{67}$, $-O-SO_2R_{68}$, or



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n) $-C(=O)NR_{59}\ R_{60}$,

o) $-NR_{56}R_{57}$,

p) $-N(R_{59})(-SO_2R_{54})$,

q) $-SO_2-NR_{59}R_{60}$,

r) $-S(=O)_iR_{54}$,

s) $-CH=N-R_{61}$, or

t) $-CH(OH)-SO_3R_{64}$;

R_{54} is the same as defined above;

R_{59} and R_{60} at each occurrence are the same or different and are

a) H,

b) C_{1-6} alkyl,

c) phenyl, or

d) tolyl;

R_{61} is

a) OH,

b) benzyloxy,

c) $-NH-C(=O)-NH_2$,

d) $-NH-C(=S)-NH_2$, or

e) $-NH-C(=NH)-NR_{62}R_{63}$;

R_{62} and R_{63} at each occurrence are the same or different and are

a) H, or

b) C_{1-4} alkyl optionally substituted with phenyl or pyridyl;

R_{64} is

a) H, or

b) a sodium ion;

R_{65} and R_{66} at each occurrence are the same or different and are

a) H,

b) formyl,

c) C_{1-4} alkyl,

d) C_{1-4} acyl,

e) phenyl,

f) C_{3-6} cycloalkyl,

g) R_{65} and R_{66} taken together are a 5-, 6-membered saturated heterocyclic moiety having one to three atoms selected from the group consisting of

S, N, and O, optionally substituted with, including on the nitrogen

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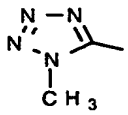
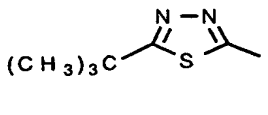
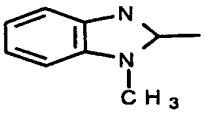
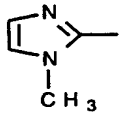
atom, phenyl, pyrimidyl, C_{1-3} alkyl, or C_{1-3} acyl,

h) $-P(O)(OR_{70})(OR_{71})$, or

i) $-SO_2-R_{72}$;

R_{67} is




or

;

R_{68} is C_{1-3} alkyl;

R_{69} is

a) C_{1-6} alkoxycarbonyl, or

b) carboxyl;

R_{70} and R_{71} at each occurrence are the same or different and are

a) H, or

b) C_{1-3} alkyl;

R_{72} is

a) methyl,

b) phenyl, or

c) tolyl;

wherein K is

a) O, or

b) S;

R_{73}, R_{74}, R_{75}, R_{76}, and R_{77} at each occurrence are the same or different and are

a) H,

b) carboxyl,

c) halo,

d) -CN,

e) mercapto,

f) formyl,

g) CF_3,

h) $-NO_2$,

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i) C_{1-6} alkoxy,

j) C_{1-6} alkoxycarbonyl,

k) C_{1-6} alkythio,

l) C_{1-6} acyl,

m) $-NR_{78}R_{79}$,

n) C_{1-6} alkyl optionally substituted with OH, C_{1-5} alkoxy, C_{1-5} acyl, $-NR_{78}R_{79}$, -N(phenyl)(CH_2-CH_2-OH), -O-CH(CH_3)(OCH_2CH_3), or -O-phenyl-[para-NHC(=O)CH_3],

o) C_{2-8} alkenylphenyl optionally substituted with R_{51},

p) phenyl optionally substituted with R_{51}, or

q) a 5-, or 6-membered (un)saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with R_{51};

R_{51} is the same as defined above;

R_{78} and R_{79} at each occurrence are the same or different and are

a) H,

b) C_{1-4} alkyl,

c) phenyl, or

d) R_{78} and R_{79} taken together with the nitrogen atom is a 5-, 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, and O, and can in turn be optionally substituted with, including on the further nitrogen atom, C_{1-3} alkyl, or C_{1-3} acyl;

wherein T is

a) O,

b) S, or

c) SO_2;

R_{75}, R_{76}, and R_{77} are the same as defined above;

R_{80} is

a) H,

b) formyl,

c) carboxyl,

d) C_{1-6} alkoxycarbonyl,

e) C_{1-8} alkyl,

f) C_{2-8} alkenyl,

wherein the substituents (e) and (f) can be optionally substituted with

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OH, halo, C_{1-6} alkoxy, C_{1-6} acyl, C_{1-6} alkylthio or C_{1-6} alkoxycarbonyl, or phenyl optionally substituted with halo,

g) an aromatic moiety having 6 to 10 carbon atoms optionally substituted with carboxyl, halo, -CN, formyl, CF_3, $-NO_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} acyl, C_{1-6} alkylthio, or C_{1-6} alkoxycarbonyl;

h) $-NR_{81}R_{82}$,

i) $-OR_{90}$,

j) $-S(=O)_i-R_{91}$,

k) $-SO_2-N(R_{92})(R_{93})$, or

l) a radical of the following formulas:

R_{81} and R_{82} at each occurrence are the same or different and are

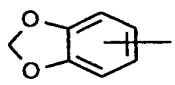
a) H,

b) C_{3-6} cycloalkyl,

c) phenyl,

d) C_{1-6} acyl,

e) C_{1-8} alkyl optionally substituted with OH, C_{1-6} alkoxy which can be substituted with OH, a 5-, or 6-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, phenyl optionally substituted with OH, CF_3, halo, $-NO_2$, C_{1-4} alkoxy, $-NR_{83}R_{84}$, or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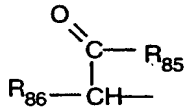
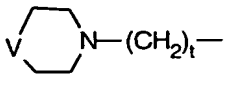
f) 
, or

g) 
;

V is

a) O,

b) CH_2, or

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c) NR_{87};

R_{83} and R_{84} at each occurrence are the same or different and are

a) H, or

b) C_{1-4} alkyl;

R_{85} is

a) OH,

b) C_{1-4} alkoxy, or

c) $-NR_{88}R_{89}$;

R_{86} is

a) H, or

b) C_{1-7} alkyl optionally substituted with indolyl, OH, mercaptyl, imidazoly, methylthio, amino, phenyl optionally substituted with OH, $-C(=O)-NH_2$, $-CO_2H$, or $-C(=NH)-NH_2$;

R_{87} is

a) H,

b) phenyl, or

c) C_{1-6} alkyl optionally substituted by OH;

R_{88} and R_{89} at each occurrence are the same or different and are

a) H,

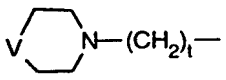
b) C_{1-5} alkyl

c) C_{3-6} cycloalky, or

d) phenyl;

R_{90} is

a) C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy or C_{1-6} hydroxy, C_{3-6} cycloalkyl, a 6-membered aromatic optionally benzo-fused heterocyclic moiety having one to three nitrogen atoms, which can in turn be substituted with one or two $-NO_2$, CF_3, halo, -CN, OH, C_{1-5} alkyl, C_{1-5} alkoxy, or C_{1-5} acyl;

b) 

,

c) phenyl, or

d) pyridyl;

R_{91} is

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a) C_{1-16} alkyl,

b) C_{2-16} alkenyl,

wherein the substituents (a) and (b) can be optionally substituted with C_{1-6} alkoxycarbonyl, or a 5-, 6-, 7-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,

c) an aromatic moiety having 6 to 10 carbon atoms, or

d) a 5-, 6-, 7-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,

wherein the substituents (c) and (d) can be optionally substituted with carboxyl, halo, -CN, formyl, CF_3, $-NO_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} acyl, C_{1-6} alkylthio, or C_{1-6} alkoxycarbonyl;

R_{92} and R_{93} at each occurrence are the same or different and are

a) H,

b) phenyl,

c) C_{1-6} alkyl, or

d) benzyl;

R_{94} and R_{95} at each occurrence are the same or different and are

a) H,

b) OH,

c) C_{1-6} alkyl optionally substituted with $-NR_{83}R_{84}$, or

d) R_{94} and R_{95} taken together are =O;

R_{96} is

a) an aromatic moiety having 6 to 10 carbon atoms,

b) a 5-, or 6-membered aromatic optionally benzo-fused heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,

wherein the substituents (a) and (b) which can in turn be substituted with one or three $-NO_2$, CF_3, halo, -CN, OH, phenyl, C_{1-5} alkyl, C_{1-5} alkoxy, or C_{1-5} acyl,

c) morpholinyl,

d) OH,

e) C_{1-6} alkoxy,

f) $-NR_{83}R_{84}$,

g) $-C(=O)-R_{97}$, or

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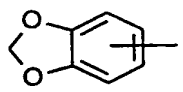
h)  ;

R_{97} is

a) morpholinyl,

b) OH, or

c) C_{1-6} alkoxy;

h is 1, 2, or 3;

i is 0, 1, or 2;

j is 0 or 1;

k is 3, 4, or 5;

l is 2 or 3;

m is 4 or 5;

n is 0, 1, 2, 3, 4, or 5;

p is 0, 1, 2, 3, 4, or 5; with the proviso that n and p together are 1, 2, 3, 4, or 5;

q is 1, 2, 3, or 4;

r is 2, 3, or 4;

t is 0, 1, 2, 3, 4, 5, or 6;

u is 1 or 2.

DETAILED DESCRIPTION OF THE INVENTION

The new compounds of the invention can be prepared using known compounds and intermediates of oxzolidinones, isoxazolines and butyolactones as intermediates and synthetic methods known in the art. Thioamides of the invention can typically be prepared by the reaction of the corresponding amide with Lawesson's reagent.

Compounds disclosed in the following publications are suitable intermediates for preparation of the compounds of this invention and are hereby incorporated by reference for their disclosure of suitable compounds that can be converted to the subject thiocarbonyl derivatives.

U.S. Patents 5,225,565; 5,182,403; 5,164,510; 5,247,090; 5,231,188; 5,565,571; 5,547,950; and 5,523,403.

PCT Application and publications PCT/US93/04850, WO94/01110; PCT/US94/08904, WO95/07271; PCT/US95/02972, WO95/25106; PCT/US95/10992, WO96/13502; PCT/US96/05202, WO96/35691; PCT/US96/12766; PCT/US96/13726;

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PCT/US96/14135; PCT/US96/17120; PCT/US96/19149; PCT/US97/01970; PCT/US95/12751, WO96/15130; and PCT/US96/00718, WO96/23788.

Chemical conversion techniques for converting various intermediates having a CH_2NH_2 on the oxazolidinone ring to CH_2NH-C(S)-CH_3 is disclosed by Hartke, K., Barrmeyer, S., J. prakt. Chem. 1996, 338, 251-6. Similarly, conversion of $CH_2NHC(=0)CH_3$ to $CH_2NHC(S)NHCH_3$ is reported by Cava, M.P.; Levinson, M.I., Thionation Reactions of Lawesson's Reagents, Tetrahedron 1985, 41, 5061-87.

For the purpose of the present invention, the carbon content of various hydrocarbon containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_{i-j} defines the number of carbon atoms present from the integer "i" to the integer "j", inclusive. Thus, C_{1-4} alkyl refers to alkyl of 1-4 carbon atoms, inclusive, or methyl, ethyl, propyl, butyl and isomeric forms thereof.

The terms "C_{1-2} alkyl", "C_{1-3} alkyl", "C_{1-4} alkyl", "C_{1-5} alkyl", "C_{1-6} alkyl", "C_{1-8} alkyl", and "C_{1-16} alkyl" refer to an alkyl group having one to two, one to three, one to four, one to five, one to six, one to eight, or one to sixteen carbon atoms respectively such as, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl and their isomeric forms thereof.

The terms "C_{2-4} alkenyl", "C_{2-5} alkenyl", "C_{2-8} alkenyl", "C_{2-14} alkenyl" and "C_{2-16} alkenyl" refer to at least one double bond alkenyl group having two to four, two to five, two to eight, two to fourteen, or two to sixteen carbon atoms, respectively such as, for example, ethenyl, propenyl, butenyl, pentenyl, pentdienyl, hexenyl, hexdienyl, heptenyl, heptdienyl, octenyl, octdienyl, octatrienyl, nonenyl, nonedienyl, nonatrienyl, undecenyl, undecdienyl, dodecenyl, tridecenyl, tetradecenyl and their isomeric forms thereof.

The terms "C_{2-5} alkynyl", "C_{2-8} alkynyl", and "C_{2-10} alkynyl" refer to at least one triple bond alkynyl group having two to five, two to eight, or two to ten carbon atoms respectively such as, for example, ethynyl, propynyl, butynyl, pentynyl, pentdiynyl, hexynyl, hexdiynyl, heptynyl, heptdiynyl, octynyl, octdiynyl, octatriynyl, nonynyl, nonediynyl, nonatriynyl and their isomeric forms thereof.

The terms "C_{3-4} cycloalkyl", "C_{3-6} cycloalkyl", "C_{5-6} cycloalkyl", and "C_{3-8} cycloalkyl" refer to a cycloalkyl having three to four, three to six, five to six, or three to eight carbon atoms respectively such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and their isomeric forms thereof.

The terms "C_{1-4} alkoxy", "C_{1-6} alkoxy", and "C_{1-8} alkoxy" refer to an alkyl

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group having one to four, one to six, or one to eight carbon atoms respectively attached to an oxygen atom such as, for example, methoxy, ethoxy, propyloxy, butyloxy, pentyloxy, hexyloxy, heptyloxy, or octyloxy and their isomeric forms thereof.

The terms "C_{1-6} alkylamino", and "C_{1-8} alkylamino" refer to an alkyl group having one to six, or one to eight carbon atoms respectively attached to an amino moiety such as, for example, methylamino, ethylamino, propylamino, butylamino, pentylamino, hexylamino, heptylamino, or octoylamino and their isomeric forms thereof.

The terms "C_{1-6} dialkylamino", and "C_{1-8} dialkylamino" refer to two alkyl groups having one to six, or one to eight carbon atoms respectively attached to an amino moiety such as, for example, dimethylamino, methylethylamino, diethylamino, dipropylamino, methypropylamino, ethylpropylamino, dibutylamino, dipentylamino, dihexylamino, methylhecylamino, diheptylamino, or dioctoylamino and their isomeric forms thereof.

The terms "C_{1-3} acyl", "C_{1-4} acyl", "C_{1-5} acyl", "C_{1-6} acyl", "C_{1-8} acyl", and "C_{2-8} acyl" refer to a carbonyl group having an alkyl group of one to three, one to four, one to five, one to six, one to eight, or two to eight carbon atoms.

The terms "C_{1-4} alkoxycarbonyl", "C_{1-6} alkoxycarbonyl", and "C_{1-8} alkoxycarbonyl" refer to an ester group having an alkyl group of one to four, one to six, or one to eight carbon atoms.

The term "C_{1-8} alkyl phenyl" refers to an alkyl group having one to eight carbon atoms and isomeric forms thereof which is substituted with at least one phenyl radical.

The term "C_{2-8} alkenyl phenyl" refers to a at least one double bond alkenyl group having one to eight carbon atoms and isomeric forms thereof which is substituted with at least one phenyl radical.

The term "C_{1-8} alkyl pyridyl" refers to an alkyl group having one to eight carbon atoms and isomeric forms thereof which is substituted with at least one pyridyl radical.

The term "C_{1-8} hydroxyl" refers to an alkyl group having one to eight carbon atoms and isomeric forms thereof attached to a hydroxy group.

The term "C_{1-8} alkylsulfonyl" refers to an alkyl group having one to eight carbon atoms and isomeric forms thereof attached to a SO_2 moiety.

The term "C_{1-6} alkylthio" refers to an alkyl group having one to six carbon atoms and isomeric forms thereof attached to a sulfur atom.

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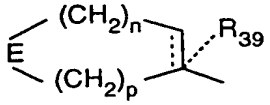
The term "Het" refers to 5 to 10 membered saturated, unsaturated or aromatic heterocyclic rings containing one or more oxygen, nitrogen, and sulfur forming such groups as, for example, pyridine, thiophene, furan, pyrazoline, pyrimidine, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 3-pyrazinyl, 2-quinolyl, 3-quinolyl, 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 2-quinazolinyl, 4-quinazolinyl, 2-quinoxalinyl, 1-phthalazinyl, 4-oxo-2-imidazolyl, 2-imidazolyl, 4-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 4-oxo-2-oxazolyl, 5-oxazolyl, 4,5,-dihydrooxazole, 1,2,3-oxathiole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isothiazole, 4-isothiazole, 5-isothiazole, 2-indolyl, 3-indolyl, 3-indazolyl, 2-benzoxazolyl, 2-benzothiazolyl, 2-benzimidazolyl, 2-benzofuranyl, 3-benzofuranyl, benzoisothiazole, benzisoxazole, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl, 3-isopyrrolyl, 4-isopyrrolyl, 5-isopyrrolyl, 1,2,3,-oxathiazole-1-oxide, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 5-oxo-1,2,4-oxadiazol-3-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 3-oxo-1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-5-yl, 2-oxo-1,3,4-thiadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,2,3,4-tetrazol-5-yl, 5-oxazolyl, 1-pyrrolyl, 1-pyrazolyl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, 1-tetrazolyl, 1-indolyl, 1-indazolyl, 2-isoindolyl, 7-oxo-2-isoindolyl,1-purinyl, 3-isothiazolyl, 4-isothiazolyl and 5-isothiazolyl, 1,3,4,-oxadiazole, 4-oxo-2-thiazolinyl, or 5-methyl-1,3,4-thiadiazol-2-yl, thiazoledione, 1,2,3,4-thiatriazole, 1,2,4-dithiazolone. Each of these moieties may be substituted as appropriate.

The term halo refers to fluoro, chloro, bromo, or iodo.

The compounds of the present invention can be converted to their salts, where appropriate, according to conventional methods.

The term "pharmaceutically acceptable salts" refers to acid addition salts useful for administering the compounds of this invention and include hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, lactate, mesylate, maleate, malate, succinate, tartrate, citric acid, 2-hydroxyethyl sulfonate, fumarate and the like. These salts may be in hydrated form.

When Q is the structure of



the dotted line in the heterocyclic ring means that this bond can be either single or double. In the case where the dotted line is a double bond, the R_{39} group will not be

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present.

The compounds of Formula I of this invention contain a chiral center at C5 of the isoxazoline ring, and as such there exist two enantiomers or a racemic mixture of both. This invention relates to both the enantiomers, as well as mixtures containing both the isomers. In addition, depending on substituents, additional chiral centers and other isomeric forms may be present in any of A or R_1 group, and this invention embraces all possible stereoisomers and geometric forms in these groups.

The compounds of this invention are useful for treatment of microbial infections in humans and other warm blooded animals, under both parenteral and oral administration.

The pharmaceutical compositions of this invention may be prepared by combining the compounds of this invention with a solid or liquid pharmaceutically acceptable carrier and, optionally, with pharmaceutically acceptable adjuvants and excipients employing standard and conventional techniques. Solid form compositions include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be at least one substance which may also function as a diluent, flavoring agent, solubilizer, lubricant, suspending agent, binder, tablet disintegrating agent, and encapsulating agent. Inert solid carriers include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, cellulosic materials, low melting wax, cocoa butter, and the like. Liquid form compositions include solutions, suspensions and emulsions. For example, there may be provided solutions of the compounds of this invention dissolved in water and water-propylene glycol and water-polyethylene glycol systems, optionally containing suitable conventional coloring agents, flavoring agents, stabilizers and thickening agents.

Preferably, the pharmaceutical composition is provided employing conventional techniques in unit dosage form containing effective or appropriate amounts of the active component, that is, the compound according to this invention.

The quantity of active component, that is the compound according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application, the potency of the particular compound, the desired concentration. Generally, the quantity of active component will range between 0.5% to 90% by weight of the composition.

In therapeutic use for treating, or combatting, bacterial infections in warm-blooded animals, the compounds or pharmaceutical compositions thereof will be

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administered orally and/or parenterally at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level of active component in the animal undergoing treatment which will be antibacterially effective. Generally, such antibacterially effective amount of dosage of active component will be in the range of about 0.1 to about 100, more preferably about 3.0 to about 50 mg/kg of body weight/day. It is to be understood that the dosages may vary depending upon the requirements of the patient, the severity of the bacterial infection being treated, and the particular compound being used. Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired blood-level or the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administration, e.g., 2-4 four times per day.

When the compounds according to this invention are administered parenterally, i.e., by injection, for example, by intravenous injection or by other parenteral routes of administration. Pharmaceutical compositions for parenteral administration will generally contain a pharmaceutically acceptable amount of the compound or a soluble salt (acid addition salt or base salt) dissolved in a pharmaceutically acceptable liquid carrier such as, for example, water-for-injection and a buffer to provide a suitably buffered isotonic solution, for example, having a pH of about 3.5-6. Suitable buffering agents include, for example, trisodium orthophosphate, sodium bicarbonate, sodium citrate, N-methylglucamine, L(+)-lysine and L(+)-arginine to name but a few representative buffering agents. The compound of this invention generally will be dissolved in the carrier in an amount sufficient to provide a pharmaceutically acceptable injectable concentration in the range of about 1 mg/mL to about 400 mg/mL of solution. The resulting liquid pharmaceutical composition will be administered so as to obtain the above-mentioned antibacterially effective amount of dosage. The compounds according to this invention are advantageously administered orally in solid and liquid dosage forms.

MIC Test Method

The in vitro MICs of test compounds were determined by a standard agar dilution method. A stock drug solution of each analog is prepared in the preferred solvent, usually DMSO:H_2O (1:3). Serial 2-fold dilutions of each sample are made using 1.0 ml aliquots of sterile distilled water. To each 1.0 ml aliquot of drug is added 9 ml of molten Mueller Hinton agar medium. The drug-supplemented agar is mixed, poured into 15 x 100 mm petri dishes, and allowed to solidify and dry prior to

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inoculation.

Vials of each of the test organisms are maintained frozen in the vapor phase of a liquid nitrogen freezer. Test cultures are grown overnight at 35°C on the medium appropriate for the organism. Colonies are harvested with a sterile swab, and cell suspensions are prepared in Trypticase Soy broth (TSB) to equal the turbidity of a 0.5 McFarland standard. A 1:20 dilution of each suspension is made in TSB. The plates containing the drug supplemented agar are inoculated with a 0.001 ml drop of the cell suspension using a Steers replicator, yielding approximately 10^4 to 10^5 cells per spot. The plates are incubated overnight at 35°C.

Following incubation the Minimum Inhibitory Concentration (MIC μg/ml), the lowest concentration of drug that inhibits visible growth of the organism, is read and recorded. The data is shown in Tables I and II.

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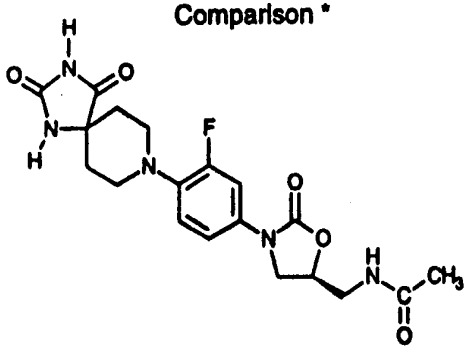
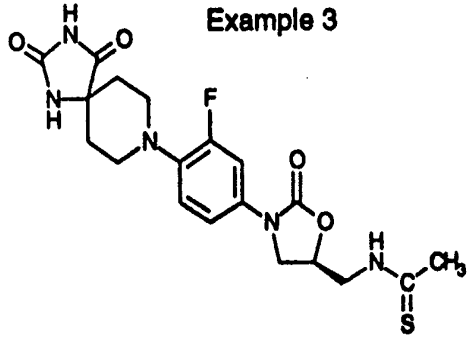
TABLE 1

Structure	Oxazolidinone MIC Values (Gram+)				
	SAUR 9213	SEPI 12084	EFAE 9217	SPNE 9912	SPYO 152
Comparison * 	16	4	8	.5	1
Example 3 	4	1	2	.25	.5

*not a compound of the subject invention

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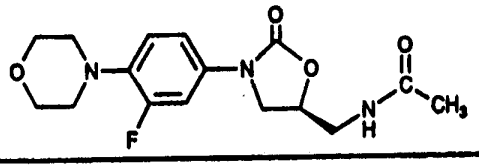
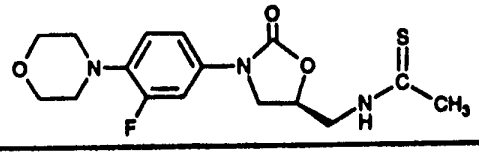
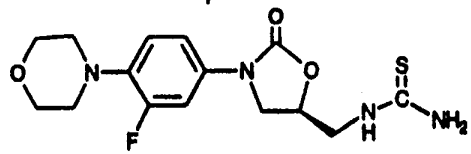
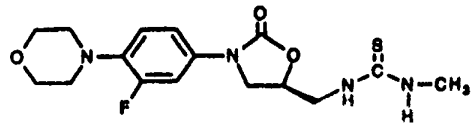
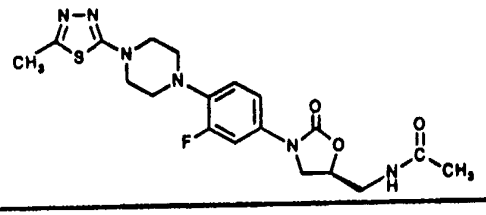
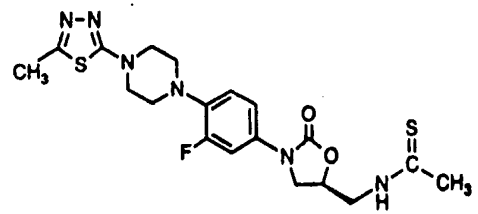
TABLE 1 (cont'd)

Structure	Oxazolidinone MIC Values (Gram+)				
	SAUR 9213	SEPI 12084	EFAE 9217	SPNE 9912	SPYO 152
Comparison * 	2	1	2	.5	1
Example 1 	1	.25	.5	.13	.13
Example 5 	1	.25	.5	<.125	.25
Example 6 	2	1	2	.5	1

not a compound of the subj ct invention

TABLE 1 (cont'd)

Structure	Oxazolidinone MIC Values (Gram+)				
	SAUR 9213	SEPI 12084	EFAE 9217	SPNE 9912	SPYO 152
Comparison * 	.5	.25	1	.13	.25
Example 2 	8	2	4	2	4

SAUR: S. *aureus*
SEPI: S. *epidermidis*
EFAE: E. *faecalis*
SPNE: S. *pneumoniae*
SPYO: S. *pyogenes*

*not a compound of the subject invention

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BNSDOCID: <WO 9854161A1 I >

TABLE II

Example No.	SAUR 9213 MIC	SEPI 30593 MIC	EFAE 12712 MIC	SPNE 9912 MIC	SPYO 152 MIC	HINF 30063 MIC	MCAT 30610 MIC	EFAE 9217 MIC
1	1	0.25	0.5	<0.125	<0.125	8	1	0.5
2	8	4	8	2	4	>16	>16	4
3	4	1	1	0.25	0.5	16	4	2
5	1	0.5	0.5	<0.125	0.25	4	2	0.5
6	2	2	2	0.5	1	16	8	2
7	0.5	0.25	0.5	<0.125	0.25	4	1	0.5
8	2	1	0.5	<0.125	0.25	4	2	1
9	0.5	0.25	0.25	<0.125	<0.125	2	0.5	0.25
10	2	1	0.5	<0.125	0.25	2	1	1
11	0.25	0.25	0.25	<0.125	0.25	2	1	0.25
12	1	0.5	0.25	<0.125	<0.125	1	0.5	0.5
13	1	1	2	0.5	1	>16	8	2
14	1	0.5	1	0.25	0.5	8	1	1
15	32	16	32	4	8	>64	64	32
16	8	8	16	2	8	>64	32	16
17	2	2	4	1	2	64	16	4
18	2	1	2	<0.5	1	32	4	2
19	32	16	32	16	16	64	32	32
21	4	4	8	2	4	64	16	8
22, 23	0.5	0.5	1	<0.125	0.25	4	2	1
24	1	0.25	0.5	<0.125	0.25	4	2	0.5
25	0.5	0.25	0.5	<0.125	<0.125	2	2	0.5
26	1	0.5	1	0.25	0.5	16	2	1

TABLE II (cont'd)

Example No.	SAUR 9213 MIC	SEPI 30593 MIC	EFAE 12712 MIC	SPNE 9912 MIC	SPYO 152 MIC	HINF 30063 MIC	MCAT 30610 MIC	EFAE 9217 MIC
27	0.5	0.5	0.5	<0.125	0.25	4	2	1
28	0.5	0.25	0.5	0.25	0.25	2	1	0.5
29	0.25	0.25	0.25	<0.125	<0.125	2	0.5	0.25
30	4	1	0.5	<0.125	0.25	8	2	1
31	2	1	1	<0.125	0.25	4	1	1
32	16	2	2	0.25	0.25	8	2	4
33	4	2	1	0.25	0.25	4	2	4
34	2	1	2	0.5	1	>16	4	2
35	1	0.5	1	0.25	0.5	16	2	1

Key:

SAUR	9213:	S. *aureus*
SEPI	30593:	S. *epidermidis*
EFAE	12712:	E. *Faecium*
SPNE	9912:	S. *pneumoniae*
SPYO	152:	S. *pyogenes*
HINF	30063:	*Haemophilus influenzae*
MCAT	30610:	*Moraxella catarrhalis*
EFAE	9217:	*Enterococcus faecalis*

As shown in Scheme 1, the intermediates **II** for the compounds of this invention are also intermediates disclosed in the oxazolidinone patents and published applications hereinabove incorporated by reference. The intermediates **IV** for this invention are final products (Examples) from the oxazolidinone patents and published applications hereinabove incorporated by reference.

As shown in Scheme 1, Step 1, and illustrated in Example 5, the isothiocyanates **III** can be conveniently prepared by allowing the amine intermediates (**II**) to react with 1,1'-thiocarbonyldi-2(1H)-pyridone in solvents such as methylene chloride at 0 to 25°C. The thioureas (**Ia**, R' = H, alkyl$_{1-4}$) can then be prepared as shown in Step 2 by the reaction of **III** with ammonia or the appropriate primary amines in solvents such as 1,4-dioxane or tetrahydrofuran at 0-50°C. Alternatively, as illustrated in Example 6 and shown in Step 3, the thioureas can be prepared by allowing **II** to react with an appropriate isothiocyanate (R' - N = C = S) in solvents such as tetrahydrofuran at 0-50°C. Thioamides (**Ib**, R" = H, alkyl$_{1-4}$) are prepared by allowing **II** to react with an appropriate dithioester (R"' S-C(=S)-R", Step 4 as illustrated in Example 4. This reaction is carried out in aqueous-alcoholic solvents at 0-50°C in the presence of an equivalent of an alkali metal hydroxide. This reaction, especially when R"' is methyl or ethyl, can be catalyzed by an alkali metal fluoride.

The reaction of II with R"'-S-C(S)-R"' (R"'=CH_3, C_2H_5) to give Ib (Step 4) can also be carried out in the presence of a tertiary amine base such as triethylamine in solvents such as THF, dioxane or methylene chloride at 10-50°C for 3-48 hr.

When the reaction conditions are tolerated by the substituents on R (see, for example, Examples 1-3) the thioamides (**Ib**, R" - H, alkyl$_{1-4}$) can also be conveniently prepared (Step 5) by allowing the appropriate amide intermediates (IV) to react with reagents such as 2,4-bis(p-methoxyphenyl)-1,3-dithiadiphosphetane-2,4-disulfide (Lawesson's Reagent) in 1,4-dioxane, benzene, toluene or tetrahydrofuran at 60-110°C; phosphorus decasulfide and sodium carbonate in tetrahydrofuran at 20-50°C [Brillon, D., Synthetic Communications, 20, 3085 (1990)] or phosphorus decasulfide and sodium fluoride in 1,2-dimethoxyethane at 20-50°C [Hartke, K., Gerber, H.-D., J. Prakt. Chem., 338, 763 (1996)].

Compounds Ic are prepared (Step 6) by allowing II to react first with carbon disulfide and a tertiary amine base such as triethylamine in solvent mixtures containing water and methanol, ethanol or isopropanol at 10-50°C for 5-24 hours. The resulting intermediate is treated with an alkylating agent (R"" X where X represents bromo, iodo, alkylsulfonyloxy or arylsulfonyloxy) at 0-30°C to give

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compounds Ic. In Step 7, compounds Ic are allowed to react with alkali metal alkoxide such as sodium methoxide or potassium ethoxide in the corresponding alkanol as solvent. This reaction is conveniently carried out at the reflux temperature of the alkanol for 1-24 hr.

5

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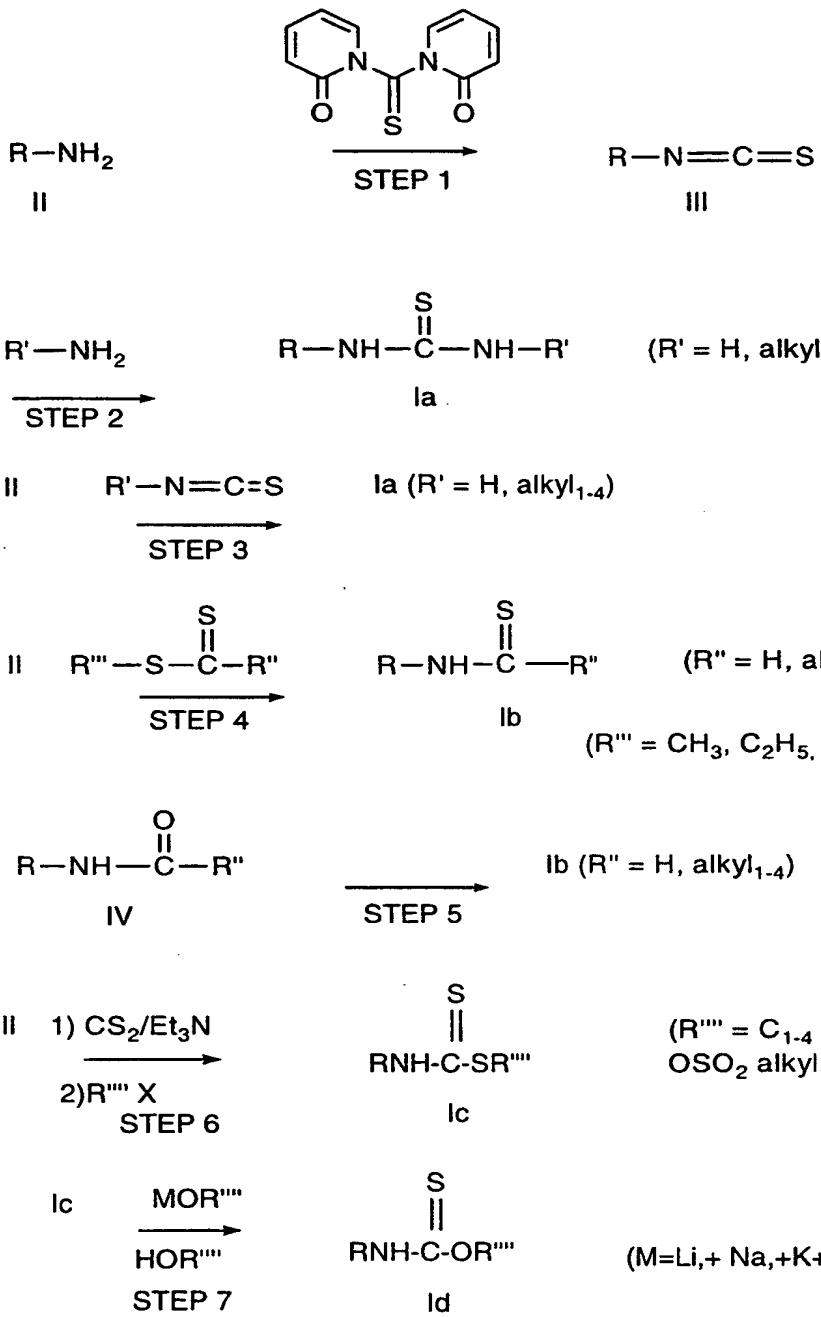
SCHEME 1



In order to more fully illustrate the nature of the invention and the manner of practicing the same, the following experimental examples are presented.

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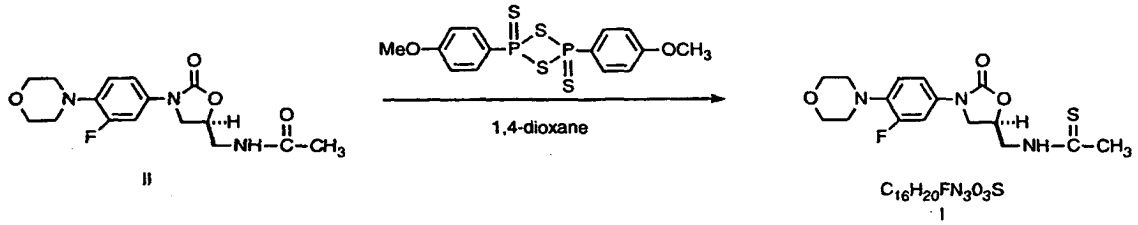
EXAMPLE 1: (*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (I)

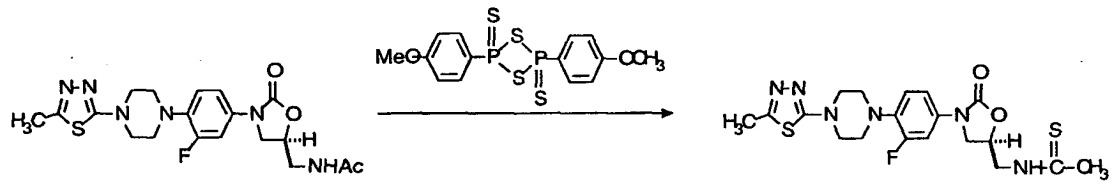


II

$C_{16}H_{20}FN_3O_3S$
I

A stirred mixture of II (PCT/US94/08904, 3.37 g, 10.0 mmol) in dry dioxane (100 mL), under nitrogen was treated with Lawesson's Reagent (4.04g, 10.0 mml), warmed to reflux during 1 h and refluxed for 1.5 h. The reaction was complete by TLC on silica gel with 10% MeOH-$CHCl_3$. It was kept at ambient temperature for 18 h and concentrated in vacuo. Chromatography of the residue on silica gel with mixtures of acetone-methylene chloride containing 10-15% acetone gave the product which was crystallized from acetone-hexane to give 1: mp 157.5-158.5 °C; HRMS theory for $C_{16}H_{20}FN_3O_3S$ (M^+): 353.1209; found: 353.1212. Anal. calcd for $C_{16}H_{20}FN_3O_3S$: C, 54.38; H, 5.38; N, 11.89; S, 9.07. Found: C, 54.21; H, 5.58; N, 11.78; S, 8.93.

EXAMPLE 2: (*S*)-N-[[3-[3-Fluoro-4-[4-(5-methyl-1,3,4-thiadiazol-2-yl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (2)



21

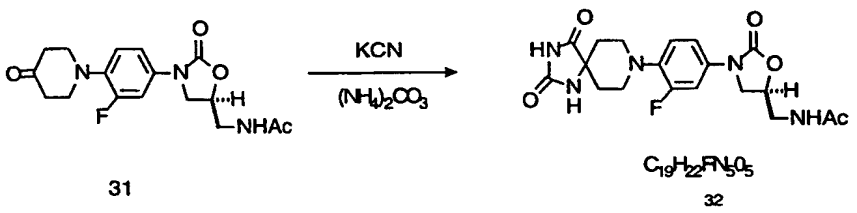
$C_{19}H_{23}FN_6O_2S_2$
2

According to Example 1, for the preparation of 1, 21 (PCT/US97/01970) was allowed to react with Lawesson's Reagent in refluxing dioxane to give 2: mp 222-223 °C; HRMS theory for $C_{19}H_{24}FN_6O_2S_2$ ($M+H^+$): 451.1386; found 451.1381.

EXAMPLE 3: (*S*)-N-[[3-[3-Fluoro-4-[2′,5′-dioxospiro[piperidine-4,4′-imidazolidine]-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (3).

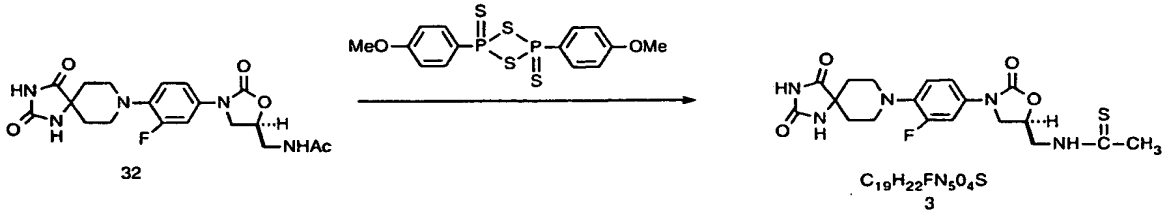
BNSDOCID: <WO___9854161A1_I_>

STEP A: (*S*)-N-[[3-[3-Fluoro-4-[2′,5′-dioxospiro[piperidine-4,4′-imidazolidine]-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (32).



A stirred suspension of 31 (Case 4780.P CP, 0.349 g, 1.00 mmol) in 1:1 EtOH:H_2O (5 mL), under nitrogen, was treated with potassium cyanide (0.130 g, 2.00 mmol) and ammonium carbonate (0.701 g, 7.30 mmol), warmed at 55-60 °C for 5 h 15 min and kept at ambient temperature for 17 h 15 min. It was then chromatographed on silica gel with mixtures of MeOH-NH_4OH-$CHCl_3$ containing 5-20% MeOH and 0.5% NH_4OH to give 0.280 g of 32: HRMS calcd for $C_{19}H_{22}FN_5O_5$: 419.1605 (M^+); found 419.1613; Anal. calcd for $C_{19}H_{22}FN_5O_5 \cdot 1\ H_2O$: C, 52.17; H, 5.53; N, 16.01. Found: C, 52.44; H, 5.30; N, 16.11.

STEP B: (*S*)-N-[[3-[3-Fluoro-4-[2′,5′-dioxospiro[piperidine-4,4′-imidazolidine]-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (3).



A stirred suspension of 32 (0.210 g, 0.500 mmol) in dioxane (5.0 mL), under nitrogen was treated with Lawesson's Reagent (0.202 g, 0.500 mmol), refluxed for 4 h and concentrated in vacuo. The residue was chromatographed on silica gel with mixtures of MeOH-NH_4OH-$CHCl_3$ containing 1-10% MeOH and 0.1-0.5% NH_4OH and the resulting product was crystallized from MeOH-$CHCl_3$-EtOAc to give 0.0491 g of 3: mp 218.5 °C; HR FAB MS theory for $C_{19}H_{22}FN_5O_4S$ (M^+): 435.1376; found 435.1370. Anal. calcd for $C_{19}H_{22}FN_5O_4S \cdot 0.5\ H_2O$: C, 51.34; H, 5.21; N, 15.76. Found: C, 51.69; H, 5.00; N, 15.25.

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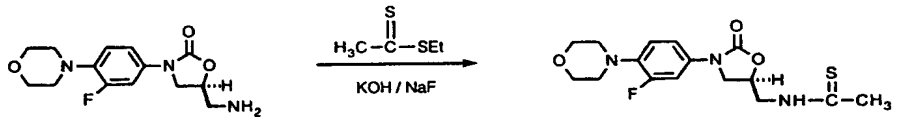
EXAMPLE 4: (*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (4).

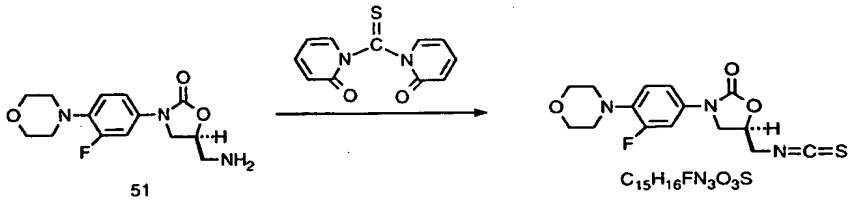


41 $C_{16}H_{20}FN_3O_3S$ 4

A solution of 41 (148 mg, 0.500 mmol) and 0.97 M KOH (0.515 mL) in absolute EtOH (5 mL) was added to a solution of ethyl dithioacetate (57 µL, 0.50 mmol) and sodium fluoride (20 mg, 0.47 mmol) in absolute EtOH (5 mL) and the mixture was kept at ambient temperature for 3 h 40 min. Additional ethyl dithioacetate (5 µL) was added after 1 h 55 min and additional 0.97 M KOH (40 mL) and sodium fluoride (6 mg) were added to the mixture after 3h 5 min. The reaction was followed by TLC on silica gel with 10% MeOH-$CHCl_3$ and 30% acetone-CH_2Cl_2. The major product had an R_f on TLC that was the same as that of 4.

EXAMPLE 5: (*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea (5).

STEP A:



51 $C_{15}H_{16}FN_3O_3S$

A solution of 51 (PCT/US94/08904, 2.07 g, 7.00 mmol) in CH_2Cl_2 was added, dropwise during 30 min, under nitrogen to an ice cold, stirred solution of 1,1′-thiocarbonyldi-2(1H)-pyridone (1.95 g, 8.40 mmol) in CH_2Cl_2 (70 mL). The mixture was warmed slowly to ambient temperature and kept for 18 h. It was then diluted with CH_2Cl_2, washed with water and aqueous NaCl, dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with 10% acetonitrile-CH_2Cl_2 gave 1.60 g of the isothiocyanate: HRMS theory for $C_{15}H_{16}FN_3O_3S$ (M^+): 337.0896; found

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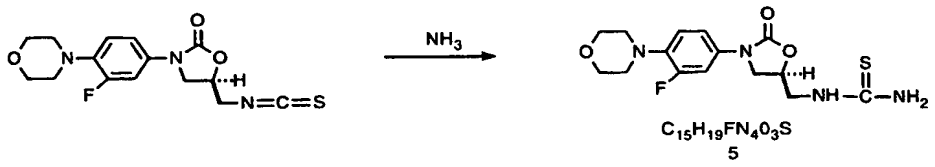
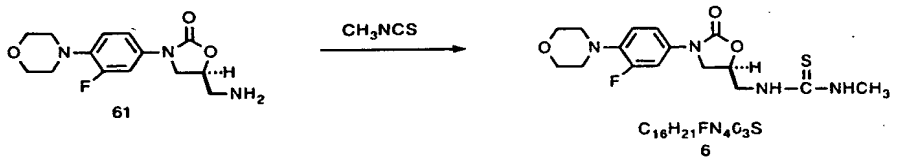
337.0888.

STEP B:



Anhydrous ammonia was bubbled for 7 min through a stirred solution of the product from Step I (1.00 g, 2.96 mmol) in THF (10 mL) and the mixture was kept at ambient temperature for 3 h 25 min and concentrated in vacuo. Crystallization of the residue from acetone-hexane gave 0.861 g of 5: mp 199-199.5 °C; MS *m/z* 354 (M^+). Anal. calcd for $C_{15}H_{19}FN_4O_3S$: C, 50.84; H, 5.40; N, 15.81. Found: C, 50.87; H, 5.39; N, 15.72.

EXAMPLE 6: (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-N′-methylthiourea (6).



A stirred solution of methyl isothiocyanate (93 mg, 1.27 mmol) in THF, was treated with 61 (295 mg, 1.00 mmol), kept at ambient temperature for 18 h and concentrated in vacuo. The residue was recrystallized from EtOAc-hexane to give 246 mg of 6: mp 158-160 °C; MS *m/z* 368 (M^+). Anal. calcd for $C_{16}H_{21}FN_4O_3S$: C, 52.16; H, 5.74; N, 15.21. Found: C, 52.20; H, 5.85; N, 15.17.

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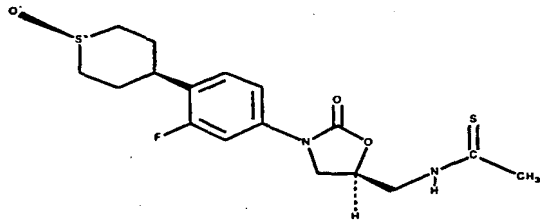
EXAMPLE 7 (S)-cis-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]ethanethioamide



Step 1: A mixture of (S)-(-)-N-[[3-[3-fluoro-4-(3,6-dihydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S-oxide (4.50 g, can be obtained according to the procedures disclosed in International Publication No. WO 97/09328) and platinum oxide (697 mg) in methanol (164 mL) is shaken on the Parr apparatus under a hydrogen atmosphere at 40 psi for 18 hours. The catalyst is then removed by filtration through Celite, and the filtrate is concentrated under reduced pressure and the residue chromatographed on silica gel (230 - 400 mesh, 350 g), eluting with a gradient of methanol/methylene chloride (3/97 - 7/93). Pooling and concentration of those fractions with an R_f = 0.44 by TLC (methanol/chloroform, 10/90) gives (S)-cis-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, mp 203 - 204°C.

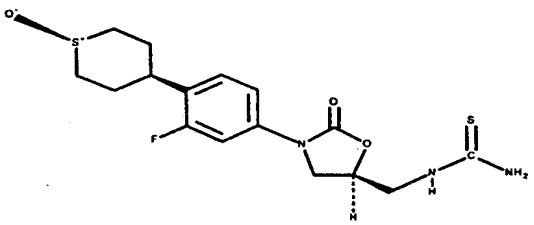
Step 2: A mixture of the compound prepared in Step 1 (2.50 g) and hydroxylamine hydrochloride (2.36 g) in pyridine (30.6 mL) and ethanol (3.4 mL) is stirred in a screw-cap vial at 100°C for 22 hrs and at ambient temperature for 16 hrs, during which additional hydroxylamine hydrochloride (944 mg) and pyridine (4 mL) is added. The reaction mixture is then concentrated under reduced pressure, diluted with saturated aqueous sodium bicarbonate (100 mL) and saline (50 mL), adjusted to pH 11 with solid sodium carbonate and extracted with methanol/methylene chloride (10/90, 5 x 100 mL). The combined organic phase is concentrated under reduced pressure, and the crude product is chromatographed on silica gel (230 - 400 mesh, 150 g), eluting with a gradient of methanol/methylene chloride (6/94 - 10/90). Pooling and concentration of those fractions with an R_f = 0.14 by TLC (methanol/chloroform, 10/90) gives (S)-cis-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, mp 159 - 161°C.

Step 3: A solution of ethyl dithioacetate (105 mL, 0.919 mmol) and sodium fluoride (39 mg, 0.919 mmol) in ethanol (9.2 mL) under a nitrogen atmosphere was treated with a mixture of (S)-cis-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-

BNSDOCID: <WO___9854161A1_I_>

yl)phenyl]-5-aminomethyl-2-oxazolidinone, as prepared in Step 2,(300 mg, 0.919 mmol) and aqueous potassium hydroxide (1M, 0.92 mL) in ethanol (46 mL). The resulting solution was stirred at ambient temperature for 4 hours and was then diluted with methylene chloride (150 mL) and washed with water (50 mL), aqueous potassium hydrogen sulfate (1M, 50 mL) and brine (25 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo*, and the crude product was triturated with methylene chloride/diethyl ether and filtered to give the title compound, mp 176 - 177°C (dec.).

EXAMPLE 8 (S)-cis-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea



Step 1: A solution of 1,1'-thiocarbonyldi-2(1H)-pyridone (235 mg, 1.01 mmol) in anhydrous methylene chloride (10 mL) at 0°C under a nitrogen atmosphere was treated with a solution of (S)-cis-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, as prepared in Example 7, Step 2, (275 mg, 0.843 mmol) in anhydrous methylene chloride (34 mL) over 30 minutes. The resulting mixture was stirred at 0°C for 30 minutes and at ambient temperature for 1 hour and was then diluted with methylene chloride (40 mL), washed with water (25 mL) and brine (25 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was chromatographed on silica gel (70 - 230 mesh, 20 g), eluting with acetonitrile/methylene chloride (40/60), and those fractions with an R_f = 0.07 by TLC (acetonitrile/methylene chloride, 30/70) were pooled and concentrated to give (S)-cis-3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-isothiocyanatomethyl-2-oxazolidinone, mp 187 - 190°C (dec.).

Step 2: A solution of (S)-cis-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-isothiocyanatomethyl-2-oxazolidinone (Step 1, 290 mg, 0.787 mmol) in anhydrous tetrahydrofuran (39 mL) at 0°C under a nitrogen atmosphere was treated

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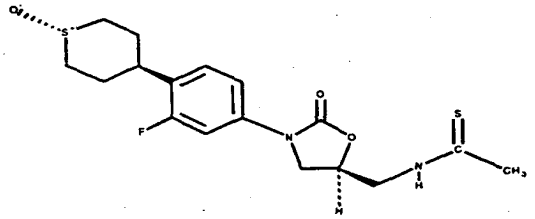
(bubbled) with a stream of ammonia gas for 5 minutes. The reaction pot was sealed, and the resulting mixture was stirred at 0°C for 1 hour. The excess ammonia was then removed under a stream of nitrogen, and the reaction mixture was concentrated *in vacuo* to give the crude product. Recrystallization from methanol/methylene chloride/diethyl ether gave the title compound, mp 206 - 208°C (dec.).

EXAMPLE 9 (S)-trans-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]ethanethioamide



Step 1: (S)-(-)-N-[[3-[3-fluoro-4-(3,6-dihydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-ox azolidinyl]methyl]acetamide S-oxide (disclosed in International Publication No. WO 97/09328) may be reduced to the corresponding cis- and trans-sulfoxides by catalytic hydrogenation in the presence of a catalyst and solvent. Alternatively, the sulfide by product of this reduction reaction can be oxidized with an oxidizing agent such $NaIO_4$ or meta-chloroperoxybenzoic acid in solvent to provide the cis- and trans-sulfoxides. The isomeric mixture can then be separated by chromatography to isolate the trans-sulfoxide, mp 211 - 212°C (dec.). A mixture of the trans-sulfoxide, (S)-trans-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, (0.90 g) and hydroxylamine hydrochloride (0.85 g) in pyridine (11.0 mL) and ethanol (1.2 mL) is stirred in a screw-cap vial at 100°C for 23 hrs and at ambient temperature for 19 hrs, during which additional hydroxylamine hydrochloride (340 mg) and pyridine (1 mL) is added. The reaction mixture is then concentrated under reduced pressure, diluted with saturated aqueous sodium carbonate (50 mL) and saline (50 mL) and extracted with methanol/methylene chloride (10/90, 6 x 100 mL). The combined organic phase is concentrated under reduced pressure, and the crude product is chromatographed on silica gel (230 - 400 mesh, 45 g), eluting with a gradient of methanol/methylene chloride (7.5/92.5 - 10/90). Pooling and concentration of those fractions with an R_f =

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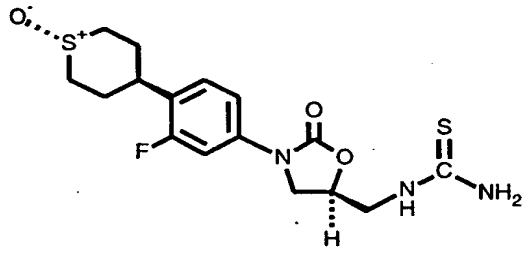
0.14 by TLC (methanol/chloroform, 10/90) gives (S)-trans-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, mp 138 - 140°C.

Step 2: A solution of ethyl dithioacetate (105 mL, 0.919 mmol) and sodium fluoride (39 mg, 0.919 mmol) in ethanol (9.2 mL) under a nitrogen atmosphere was treated with a mixture of (S)-trans-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, as prepare in Step 1, (300 mg, 0.919 mmol) and aqueous potassium hydroxide (1M, 0.92 mL) in ethanol (46 mL). The resulting solution was stirred at ambient temperature for 17 hours and was then diluted with methylene chloride (150 mL), washed with water (2 x 50 mL) and brine (25 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was chromatographed on silica gel (230 - 400 mesh, 35 g), eluting with methanol/methylene chloride (3/97), and those fractions with an R_f = 0.56 by TLC (methanol/chloroform, 10/90) were pooled and concentrated and the residue recrystallized from methylene chloride/diethyl ether to give the title compound, mp 193 - 194°C (dec.).

EXAMPLE 10 (S)-trans-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea



Step 1: A solution of 1,1'-thiocarbonyldi-2(1H)-pyridone (192 mg, 0.827 mmol) in anhydrous methylene chloride (8.3 mL) at 0°C under a nitrogen atmosphere was treated with a solution of (S)-trans-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, as prepared in Example 9, Step 1, (225 mg, 0.689 mmol) in anhydrous methylene chloride (28 mL) over 30 minutes. The resulting mixture was stirred at 0°C for 30 minutes and at ambient temperature for 40 minutes and was then diluted with methylene chloride (20 mL), washed with water (15 mL) and brine (15 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was chromatographed on silica gel (32 - 63 mm, 40 g), eluting with a gradient of acetonitrile/methylene chloride (30/70 -

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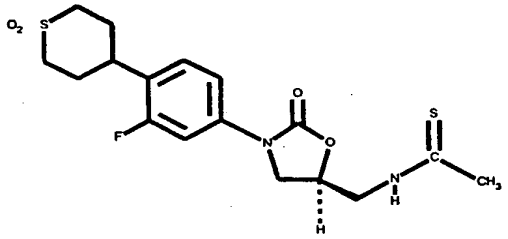
60/40) under 15 psi N_2, and those fractions with an $R_f = 0.12$ by TLC (acetonitrile/methylene chloride, 30/70) were pooled and concentrated to give (S)-trans-3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4- yl)phenyl]-5-isothiocyanatomethyl-2-oxazolidinone, mp 165 - 167°C.

Step 2: A solution of (S)-trans-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-isothiocyanatomethyl-2-oxazolidinone (Step 1, 230 mg, 0.624 mmol) in anhydrous tetrahydrofuran (31.2 mL) at 0°C under a nitrogen atmosphere was treated (bubbled) with a stream of ammonia gas for 5 minutes. The reaction pot was sealed, and the resulting mixture was stirred at 0°C for 1 hour. The excess ammonia was then removed under a stream of nitrogen, and the reaction mixture was concentrated *in vacuo* to give the crude product. Trituration with methanol/methylene chloride/diethyl ether gave the title compound, mp 209 - 210°C (dec.).

EXAMPLE 11 (S)-N-[[3-[3-Fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]ethanethioamide



Step 1: Starting with (S)-cis-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as prepared in Example 7, Step 1, and following the general procedure of Step 2, and making non-critical variations by substituting (S)-(-)-N-[[3-[3-fluoro-4-(tetrahydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S,S-dioxide (disclosed in International Publication No. WO 97/09328) for (S)-cis-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, the product (S)-(-)-3-[3-Fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone is obtained, mp 194°C (dec.).

Step 2: A solution of ethyl dithioacetate (100 mL, 0.876 mmol) and sodium fluoride (37 mg, 0.876 mmol) in ethanol (8.8 mL) under a nitrogen atmosphere was

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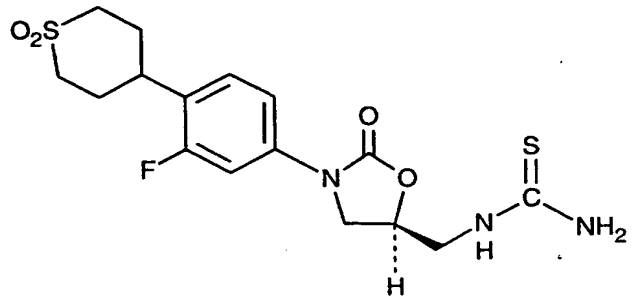
treated with a mixture of (S)-(-)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, as prepared in Step 1, (300 mg, 0.876 mmol) and aqueous potassium hydroxide (1M, 0.88 mL) in ethanol (43.8 mL). The resulting mixture was stirred at ambient temperature for 26 hours, during which additional ethyl dithioacetate (50 mL, 0.438 mmol), sodium fluoride (19 mg, 0.438 mmol), aqueous potassium hydroxide (1M, 0.44 mL) and ethanol (3.0 mL) was added, and was then diluted with methylene chloride (150 mL), washed with water (50 mL), aqueous potassium hydrogen sulfate (1M, 50 mL) and brine (25 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was recrystallized from methylene chloride/diethyl ether to give the title compound, mp 186 - 187°C (dec.).

EXAMPLE 12 (S)-N-[[3-[3-Fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea



Step 1: A solution of 1,1'-thiocarbonyldi-2(1H)-pyridone (304 mg, 1.31 mmol) in anhydrous methylene chloride (13 mL) at 0°C under a nitrogen atmosphere was treated with a solution of (S)-(-)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, as prepared in Example 11, Step 1, (375 mg, 1.09 mmol) in anhydrous methylene chloride (88 mL) over 30 minutes. The resulting mixture was stirred at 0°C for 30 minutes and at ambient temperature for 30 minutes and was then diluted with methylene chloride (40 mL), washed with water (25 mL) and brine (25 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was chromatographed on silica gel (230 - 400 mesh, 45 g), eluting with acetonitrile/methylene chloride (7.5/92.5), and those fractions with an R_f = 0.64 by TLC (acetonitrile/methylene chloride, 20/80) were pooled and concentrated to give (S)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-5-isothiocyanatomethyl-2-oxazolidinone, mp 158 - 162°C (dec.).

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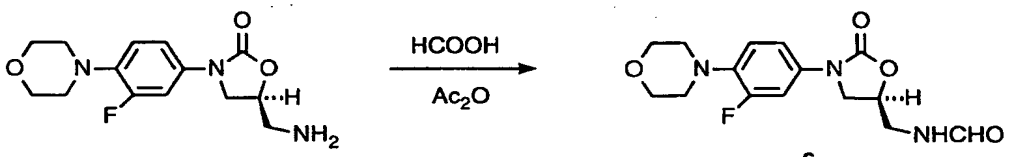
Step 2: A solution of (S)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-5-isothiocyanatomethyl-2-oxazolidinone (Step 1, 380 mg, 0.988 mmol) in anhydrous tetrahydrofuran (49 mL) at 0°C under a nitrogen atmosphere was treated (bubbled) with a stream of ammonia gas for 5 minutes. The reaction pot was sealed, and the resulting mixture was stirred at 0°C for 1 hour. The excess ammonia was then removed under a stream of nitrogen, and the reaction mixture was concentrated *in vacuo* to give the crude product. Recrystallization from methanol/methylene chloride/diethyl ether gave the title compound, mp 196 - 198°C (dec.).

EXAMPLE 13: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-thioformamide (7).**

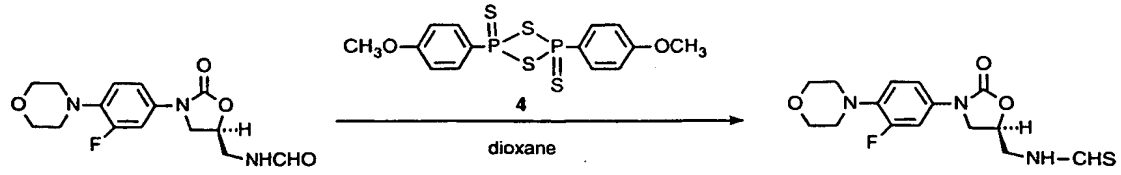
1.



39 6

A stirred mixture of acetic anhydride (0.23 mL, 0.0024 mol) and 95-97% formic acid (0.10 mL, 0.0027 mL) was warmed, under nitrogen at 50-55 °C for 2 h, cooled to ambient temperature and treated, portionwise during 2 min, with **39**[8] (0.45 g, 0.0015 mol). The suspension was kept at ambient temperature for 4 h and the resulting solution was treated with Et_2O (1 mL) and kept at ambient temperature for 18 h. The mixture was diluted with additional Et_2O (10 mL) and the solid was collected by filtration, washed with Et_2O and dried to give 0.38 g of **6**[9]: MS (ES) *m/z* 324 ($M+H^+$), 346 ($M+Na^+$); ^1H NMR (300 mHz, $CDCl_3$) d 3.08 (m, 4H), 3.72 (m, 2H), 3.77 (d,d, 1H), 3.89 (m, 4H), 4.04 (t, 1H), 4.80 (m, 1H), 6.33 (s, 1H), 7.05 (m, 2H), 7.45 (d,d, 1H), 8.27 (s, 1H).

2.



6 7

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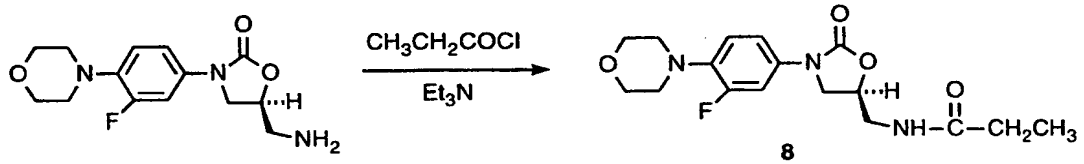
A stirred mixture of **6** (0.38 g, 0.00118 mol) in dioxane (20 mL), under nitrogen was treated with 4 (0.51 g, 0.00126 mol), warmed to reflux during 30 min and kept at this temperature for 90 min. It was then evaporated under a stream of nitrogen. The residue was chromatographed on silica gel with 1.25% MeOH-CH_2Cl_2 and the slightly impure product was rechromatographed on silica gel with 25% EtOAc-CH_2Cl_2. The resulting product was crystallized from EtOAc-methyl *tert*-butyl ether to give 0.114 g of **7**: mp 150-155 °C (dec); IR (DRIFT) 3322, 1752 cm^{-1}; MS(ES) *m/z* 340 ($M+H^+$), 362 ($M+Na^+$); ^{1}HNMR [300 MHz, $(CD_3)_2SO$] d 2.94 (m, 4H), 3.72 (m, 4H), 3.77 (d,d, 1H), 3.94 (t, 2H), 4.12 (t, 1H), 4.93 (m, 1H), 7.05 (t, 1H), 7.16 (d,d, 1H), 7.47 (d,d, 1H), 9.33 (d, 1H), 10.59 (s, 1H). Anal. calcd for $C_{15}H_{18}FN_3O_3S$: C, 53.08; H, 5.35; N, 12.38. Found: C, 53.02; H, 5.44; N, 12.36.

EXAMPLE 14: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiopropion-amide (9).**

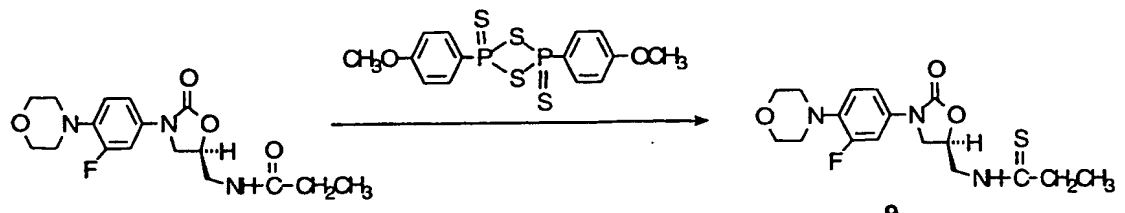
1.



39 8

An ice cold, stirred solution of **39**[8] (0.395 g, 0.00134 mol) and triethyl amine (0.186 mL, 0.0027 mol) in CH_2Cl_2 (20 mL), under nitrogen was treated, dropwise during 2 min, with a solution of propionyl chloride (0.128 mL, 0.00147 mol) in CH_2Cl_2 (3 mL). The mixture was kept in the ice bath for 20 min and at ambient temperature for 1 h. It was then diluted with CH_2Cl_2, washed with saturated $NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated. The residue (**8**)[9] was used without further purification in the next reaction.

2.



8 9

A stirred mixture of the product (**8**) from the previous reaction and dioxane (20 mL), under nitrogen, was treated, portionwise during 1 min, with Lawesson's reagent

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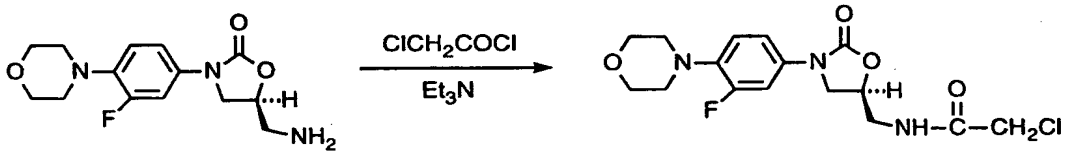
(0.58 g, 0.0014 mol) and refluxed for 2 h; it was then concentrated. The residue was chromatographed on silica gel with 2% MeOH-$CHCl_3$ and the product was crystallized from methyl *tert*-butyl ether to give 0.259 g of **9**: mp 138-139 °C; MS(ES) *m/z* 368 ($M+H^+$), 390 ($M+Na^+$); IR (DRIFT) 3284, 3266, 1748, 1744 cm^{-1}; $[\alpha]^{24}_D$ +20° (MeOH); 1H NMR[300 MHz, $(CD_3)_2SO$] d 1.12 (t, 3H), 2.56 (q, 2H), 2.94 (m, 4H), 3.72 (m, 4H), 3.78 (d,d, 1H), 3.90 (t, 2H), 4.11 (t, 1H), 4.93 (m, 1H), 7.05 (t, 1H), 7.16 (d,d, 1H), 7.47 (d,d, 1H), 10.30 (broad s, 1H). Anal. calcd for $C_{17}H_{22}FN_3O_3S$: C, 55.57; H, 6.03; N, 11.44. Found: C, 55.68; H, 6.21; N, 11.37.

EXAMPLE 15: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-2-chlorothioacetamide (11).**

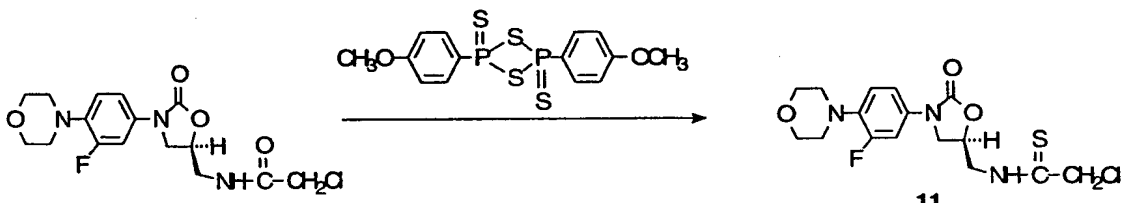
1.



39 10

A stirred solution of **39** (1.54 g, 5.2 mmol) and triethylamine (750 mg, 7.5 mmol) in CH_2Cl_2 (50 mL), under nitrogen, was treated, dropwise, during 15 min with a solution of chloroacetyl chloride (465 mL, 5.8 mmol) in CH_2Cl_2 (30 mL) and kept at ambient temperature for 18 h. It was then washed with saturated $NaHCO_3$ and dilute NaCl, dried (Na_2SO_4) and concentrated. The residue was flash chromatographed on silica gel with 20-30% acetone-CH_2Cl_2 to give 1.49 g of **10**[9] which was used in the next reaction without further purification.

2.



10 11

A stirred mixture of **10** (0.371 g, 1.0 mmol) and Lawesson's reagent (0.420 mg, 1.04 mmol) in dioxane (10 mL) was refluxed, under nitrogen for 2 h and concentrated under reduced pressure. The residue was chromatographed on silica gel with 3-10% acetone-CH_2Cl_2 to give 0.143 g of **11**: MS (CI) *m/z* 388 ($M+H^+$); ^1H NMR (300 MHz, $CDCl_3$) d 3.07 (m, 4H), 3.77 (d,d, 1H), 3.88 (m, 4H), 4.04 (m, 1H), 4.12 (t, 1H),

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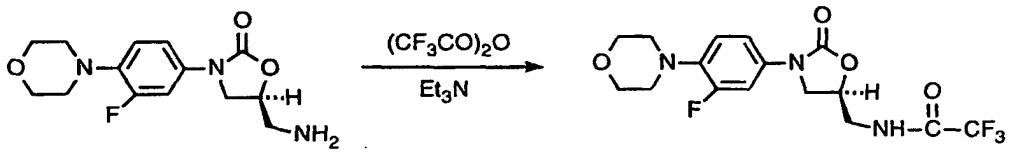
4.35 (m, 1H), 4.61 (s, 2H), 4.98 (m, 1H), 6.96 (t, 1H), 7.08 (d,d, 1H), 7.44 (d,d, 1H), 8.69 (s, 1H). Anal. calcd for $C_{16}H_{19}ClFN_3O_3S$: C, 49.55; H, 4.94; N, 10.83. Found: C, 49.38; H, 5.20; N, 10.27.

EXAMPLE 16: **(*S*)-N-[[3-[3-Fluoro-4-(4-moropholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α,α,α-trifluorothioacetamide (13).**

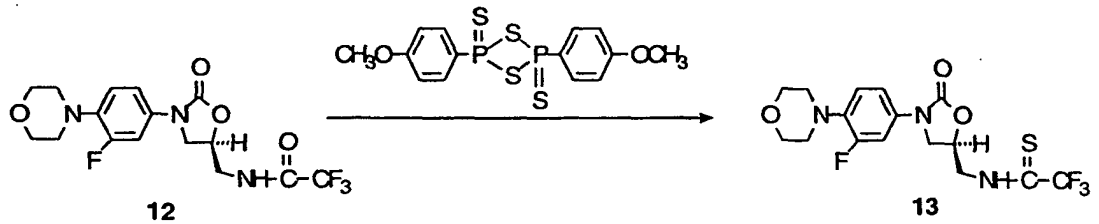
1.



39 12

An ice cold stirred solution of **39** (0.590 g, 2.0 mmol) and triethylamine (640 mL, 4.6 mmol) in CH_2Cl_2 (10 mL) was treated with trifluoroacetic anhydride (325 mL, 2.3 mmol) and kept in the ice bath for 10 min and then at ambient temperature. The reaction was followed by TLC on silica gel with 30% acetone-CH_2Cl_2. Additional trifluoroacetic anhydride and triethylamine were added after 3 d (64 mL / 125 mL), 4 d (100 mL / 220 mL) and 6 d (325 mL / 1.0 mL). The reaction was complete 1 h after the last addition; it was mixed with CH_2Cl_2, washed with water and dilute NaCl, dried (Na_2SO_4) and concentrated. The solid residue was recrystallized from acetone-heptane to give 0.566 g of **12**: mp 161-164 °C (dec); MS(EI) *m/z* 391 (M^+). Anal. calcd for $C_{16}H_{17}F_4N_3O_4$: C, 49.11; H, 4.38; N, 10.74. Found: C, 48.99; H, 4.56; N, 10.73.

2.



12 13

A stirred mixture of **12** (0.391 g, 1.0 mmol) and Lawesson's reagent (0.422 g, 1.1 mmol) in dioxane (10 mL) was refluxed, under nitrogen for 2 h, cooled slowly to ambient temperature and concentrated in vacuo. The residue was flash chromatographed on silica gel with 5-15% acetone-CH_2Cl_2 and the product was crystallized from acetone-heptane to give 0.249 g of **13**: mp 151-152 °C; MS(EI) *m/z* 407 (M^+), 363, 209, 151, 95; ^1H NMR (300 MHz, $CDCl_3$) d 3.05 (m, 4H), 3.75 (d,d,

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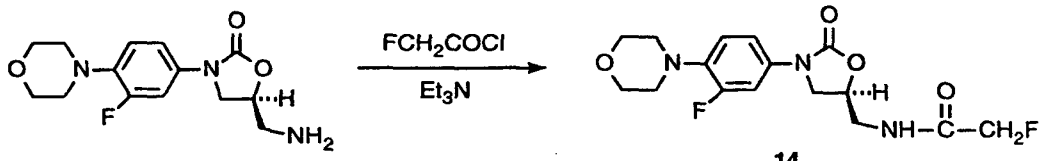
1H), 3.87 (m, 4H), 3.95 (m, 1H), 4.14 (t, 1H), 4.32 (m, 1H), 5.01 (m, 1H), 6.92 (t, 1H), 7.05 (d,d, 1H), 7.38 (d,d, 1H), 9.03 (s, 1H). Anal. calcd for $C_{16}H_{17}F_4N_3O_3S$: C, 47.17; H, 4.21; N, 10.31. Found: C, 47.09; H, 4.35; N, 10.27.

EXAMPLE 17: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α-fluorothioacetamide (15).**

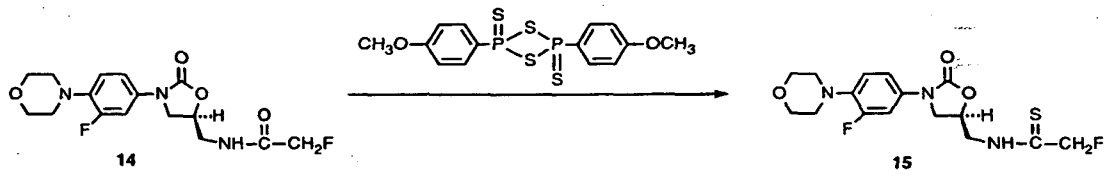
1.



39 14

A stirred, ice cold solution of **39** (0.590 g, 2.0 mmol) and triethylamine (611 mL, 4.4 mmol) in CH_2Cl_2 (10 mL), under nitrogen, was treated, dropwise, with a solution of fluoroacetyl chloride (220 mL, 2.2 mmol) in CH_2Cl_2 (5 mL), kept in the ice bath for 10 min and at ambient temperature for 2 h. It was then diluted with CH_2Cl_2, washed with water and dilute NaCl, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with 10-30% acetone-CH_2Cl_2 to give 0.180 g of **14**: MS(ES) *m/z* 356 ($M+H^+$), 378 ($M+Na^+$).

2.



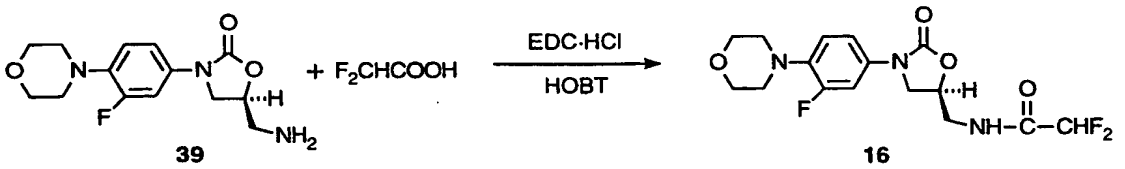
14 15

A solution of **14** (0.180 g, 0.507 mmol) in dioxane, under nitrogen, was treated with Lawesson's reagent (0.206 g, 0.51 mmol), warmed at 90-100 °C for 1 h and concentrated in vacuo. The residue was chromatographed on silica gel with 15% acetone-CH_2Cl_2 to give 0.161 g of **15**: MS(EI) *m/z* 371 (M^+); ^1H NMR (300 MHz, $CDCl_3$) d 3.05 (m, 4H), 3.78 (d,d, 1H), 3.87 (m, 4H), 4.03 (m, 1H), 4.11 (t, 1H), 4.38 (m, 1H), 4.98 (m, 1H), 5.07 (s, 1H), 5.23 (s, 1H), 6.93 (t, 1H), 7.08 (dd, 1H), 7.42 (d,d, 1H), 8.42 (s, 1H). Anal. calcd for $C_{16}H_{19}F_2N_3O_3S$: C, 51.74; H, 5.16; N, 11.31. Found: C, 51.79; H, 5.31; N, 11.02.

EXAMPLE 18: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α,α-difluorothioacetamide (17).**

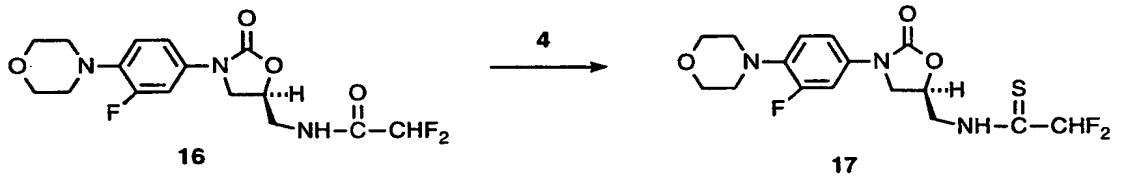
BNSDOCID: <WO 9854161A1_I_>

1.



A stirred, ice cold mixture of **39** (0.590 g, 2.0 mmol), difluroacetic acid (190 mL, 2.0 mmol), and 1-hydroxybenzotriazole (0.297 g, 2.2 mmol) in DMF (5 mL) under nitrogen, was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.843 g, 4.4 mmol) and kept at ambient temperature for 18 h. It was diluted with CH_2Cl_2, washed with water and dilute NaCl, dried (Na_2SO_4) and concentrated. The solid residue was crystallized form EtOAc-heptane to give 0.617 g of **16**: mp 149-150 °C; 1H NMR (300 MHz, CDCl3) d 3.05 (m, 4H), 3.66 (m, 2H), 3.85 (m, 5H), 4.08 (t, 1H), 4.80 (m, 1H), 5.93 (t, J = 53.9 Hz, 1H), 6.92 (t, 1H), 7.06 (m, 2H), 7.39 (d,d, 1H); MS(EI) m/z 373 (M^+). Anal. calcd for $C_{16}H_{18}F_3N_3O_4$: C, 51.48; H, 4.86; N, 11.26. Found: C, 51.59; H, 4.91; N, 11.29.

2.

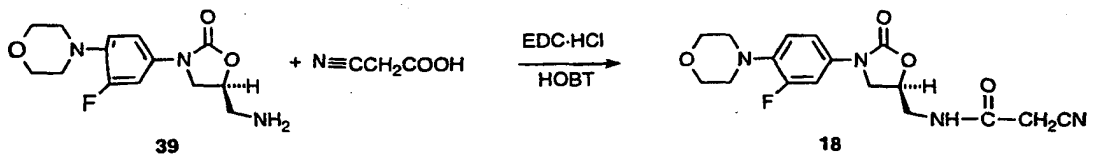


A stirred solution of **16** (0.373 g, 1.00 mmol) in dioxane (10 mL), under nitrogen was treated with Lawesson's reagent (0.404 g, 1.00 mmol), warmed at about 95 °C for 1 h and concentrated in vacuo. Chromatography of the residue on silica gel with 10% acetone-CH_2Cl_2 and cyrstallization of the product from EtOAc-heptane gave 0.276 g of **17**: mp 125-127 °C; MS(EI) m/z 389 (M^+), 345, 305, 247, 209, 195, 151, 138, 123, 109, 95; ^1H NMR (300 MHz, $CDCl_3$) d 3.05 (m, 4H), 3.76 (d,d, 1H), 3.86 (m, 4H), 4.01 (m, 1H), 4.12 (t, 1H), 4.30 (m, 1H), 4.99 (m, 1H), 6.20 (t, J = 55.9 Hz, 1H), 6.92 (t, 1H), 7.06 (d,d, 1H), 7.38 (d,d, 1H), 8.78 (broad s, 1H). Anal. calcd for $C_{16}H_{18}F_3N_3O_3S$: C, 49.35; H, 4.66; N, 10.79. Found: C, 49.37; H, 4.71; N, 10.83.

EXAMPLE 19: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α-cyanothioacetamide (19).**

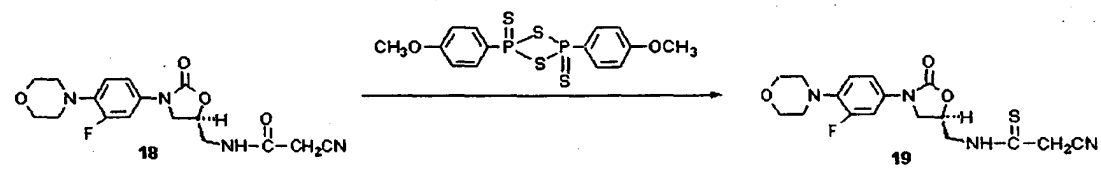
BNSDOCID: <WO___9854161A1_I_>

1.



An ice cold, stirred mixture of **39** (0.646 g, 2.19 mmol), cyanoacetic acid (0.179 g, 2.1 mmol) and 1-hydroxybenzotriazole (0.351 g, 2.6 mmol) in DMF (5 mL), under nitrogen, was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.997 g, 5.2 mmol) and kept at ambient temperature for 24 h. It was diluted with CH_2Cl_2, washed with water and dilute NaCl, dried (Na_2SO_4) and concentrated. The solid residue was crystallized from EtOAc-heptane to give 0.546 g of **18**: mp 172-174 °C: IR (DRIFT) 3316, 2256, 1754, 1684 cm^{-1}; MS(EI) *m/z* 362 (M^+). Anal. calcd for $C_{17}H_{19}FN_4O_4$: C, 56.35; H, 5.28; N, 15.46. Found: C, 56.33; H, 5.30; N, 15.36.

2.

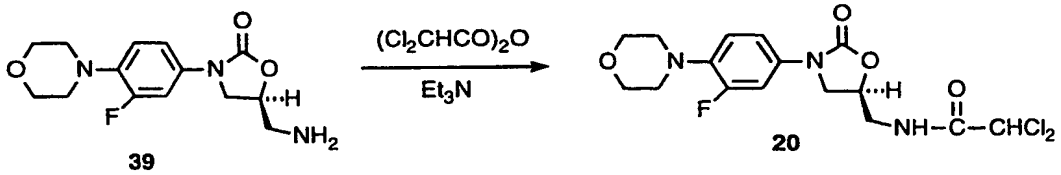


A stirred solution of **18** (0.453 mg, 1.25 mmol) in dioxane (10 mL), under nitrogen, was treated with Lawesson's reagent (0.505 g, 1.25 mmol) and warmed at about 100 °C. When the reaction was over (TLC with 30% acetone-CH_2Cl_2) the mixture was cooled and concentrated in vacuo. Chromatography of the residue on silica gel with 10-20% acetone-CH_2Cl_2 and crystallization of the product from EtOAc-heptane gave 0.110 g of **19**: mp 186-187 °C (dec); MS(ES) *m/z* 379 ($M+H^+$), 401 ($M+Na^+$); ^1H NMR (300 MHz, $CDCl_3$) d 3.05 (m, 4H), 3.81 (d,d, 1H), 3.86 (m, 4H), 3.89 (s, 2H), 4.09 (t, 1H), 4.14 (m, 2H), 5.01 (m, 1H), 6.92 (t, 1H), 7.05 (d,d, 1H), 7.34 (d,d, 1H), 9.15 (s, 1H); IR (DRIFT) 3244, 2260, 1754 cm^{-1}. Anal. calcd for $C_{17}H_{19}FN_4O_3S$: C, 53.96; H, 5.06; N, 14.81. Found: C, 53.88; H, 5.39; N, 14.61.

EXAMPLE 20: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α,α-dichlorothioacetamide (21).**

BNSDOCID: <WO 9854161A1 I >

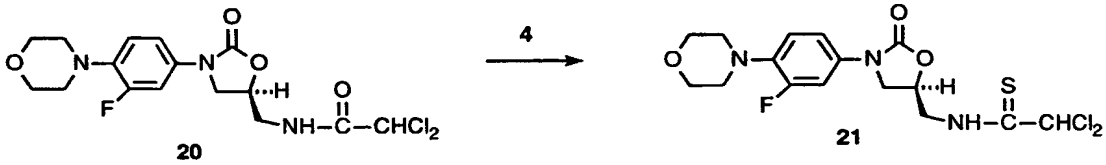
1.



39 20

A stirred, ice cold solution of **39** (0.885 g, 3.00 mmol) and triethylamine (975 mL, 7 mmol) in CH_2Cl_2 (15 mL), under nitrogen was treated, dropwise with a solution of dichloroacetic anhydride (555 mL, 3.5 mmol) in CH_2Cl_2 (5 mL) and kept in the ice bath for 15 min and at ambient temperature for 18 h. It was diluted with CH_2Cl_2, washed with water, saturated $NaHCO_3$ and dilute NaCl, dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with 10% acetone-CH_2Cl_2 and crystallization of the product from acetone-heptane gave 0.463 g of **20**: mp 197-198 °C (dec); MS(ES) *m/z* 406 ($M+H^+$), 428 ($M+Na^+$); ^1H NMR (300 MHz, $CDCl_3$) d 3.05 (m, 4H), 3.75 (m, 3H), 3.86 (m, 4H), 4.07 (t, 1H), 4.83 (m, 1H), 5.94 (s, 1H), 6.92 (t, 1H), 7.06 (m, 2H), 7.41 (d,d, 1H).

2.

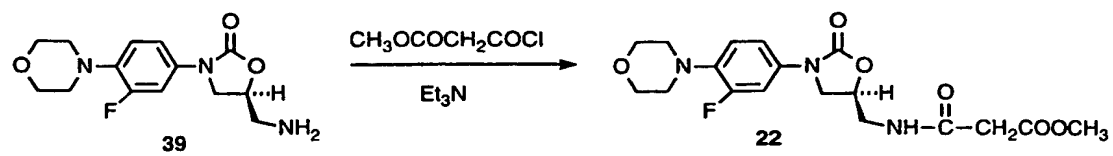


20 21

A stirred solution of **20** (0.305g, 0.75 mmol) in dioxane (5 ml), under nitrogen, was treated with Lawesson's reagent (0.202g, 0.5 mmol), warmed at about 90°C for 1 hour, cooled and concentrated in vacuo. Chromatography of the residue on silica gel first with 30% acetone-heptane and then with 10% acetone-methylene chloride and crystallization of rh product form methylene chloride - heptane gave 0.203g with **21**: mp 143-144°cd.; HR17S (EI) calculated for $C_{16}H_{18}cl_2$ F N_3 O_3 S(M) 421.0431. Anal. calcd for $C_{16}H_{18}cl_2$ F N_3 O_3 S, C, 45.51; H, 4.30; N, 9.95. Found: C, 45.47; H, 4.24; H, 9.88.

EXAMPLE 21: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α-(methoxycarbonyl)thioacetamide (23).**

1.



39 22

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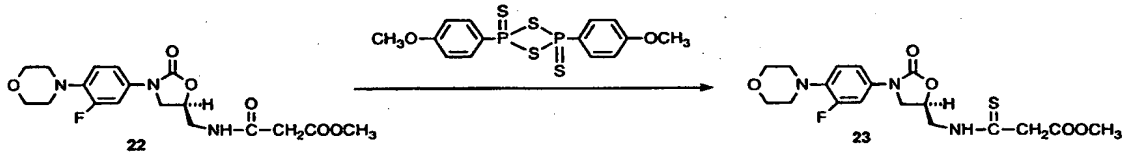
A stirred solution of **39** (0.955 g, 3.2 mmol) and triethylamine (650 mL, 4.5 mmol) in CH_2Cl_2 (50 mL), under nitrogen, was treated, dropwise during 15-20 min with a solution of methyl malonyl chloride (475 mL, 4.3 mmol) in CH_2Cl_2 (10 mL) and kept at ambient temperature for 3 days. It was then washed with water and dilute NaCl, dried and concentrated. The residue was flash chromatographed on silica gel with 15-30% acetone-CH_2Cl_2 and the product was crystallized form acetone-hexane to give 0.873 g of **22**: mp 150-151 °C; ^{1}H NMR (300 MHz, $CDCl_3$) d 3.03 (m, 4H), 3.34 (s, 2H), 3.67 (s, 3H), 3.69 (m, 2H), 3.76 (d,d, 1H), 3.85 (m, 4H), 4.00 (t, 1H), 4.78 (m, 1H), 6.90 (t, 1H), 7.06 (d,d, 1H), 7.41 (d,d, 1H), 7.57 (t, 1H); MS(ES) *m/z* 396 ($M+H^+$), 418 ($M+Na^+$); HRMS (FAB) calcd for $C_{18}H_{23}FN_3O_6$ ($M+H^+$) 396.1571, found 396.1579. Anal. calcd for $C_{18}H_{22}FN_3O_6$: C, 54.68; H, 5.61; N, 10.63. Found: C, 54.69; H, 5.68; N, 10.58.

2.



A stirred solution of **22** (0.395 g, 1.0 mmol) in dioxane (10 mL), under nitrogen, was treated with Lawesson's reagent (0.202 g, 0.5 mmol) and kept at ambient temperature for 4 h 10 min and at 80-90 °C for 1.5 h. The reaction was followed by TLC on silica gel with 10% MeOH-$CHCl_3$. At this time a new, less polar product had begun to form. It was kept at ambient temperature for 18 h and at 80 °C for 2 h; additional Laewsson's reagent (40 mg, 0.099 mmol) was added and warming at 80 °C was continued for 2 h; some starting material still remained. The mixture was concentrated and the residue was chromatographed on silica gel with 15% acetone-CH_2Cl_2 to give 0.348 g of **23**: ^{1}H NMR (300 MHz, $CDCl_3$) d 3.05 (m, 4H), 3.71 (s, 3H), 3.81 (d,d, 1H), 3.86 (m, 4H), 3.88 (s, 2H), 4.07 (t, 1H), 4.19 (m, 2H), 4.99 (m, 1H), 6.91 (t, 1H), 7.07 (d,d, 1H), 7.42 (d,d, 1H), 9.52 (s, 1H); IR (DRIFT) 3269, 1743 cm^{-1}; MS(EI) *m/z* 411 (M^+). Anal. calcd for $C_{18}H_{22}FN_3O_5S$: C, 52.54; H, 5.39; N, 10.21. Found: C, 52.58; H, 5.43; N, 10.14.

EXAMPLE 22: **(*S*)-N-[[3-[4-[1-[1,2,4]Triazolyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (25).**

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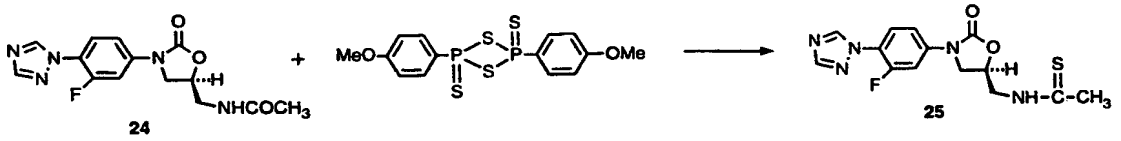
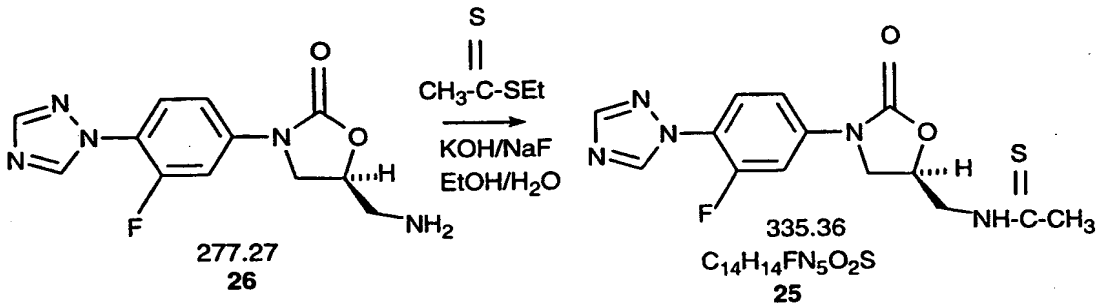


24 25

A stirred mixture of **24**[10,11] (0.150 g, 0.470 mmol) and dioxane (12.5 mL), under nitrogen, was treated with Lawesson's reagent (0.20 g, 0.50 mmol), refluxed for 1.5 h, kept at ambient temperature for 18 h and concentrated in vacuo. Flash chromatography of the residue on silica gel with 5% MeOH-$CHCl_3$ gave the product which was crystallized from MeOH to give 0.100 g (63.4%) of **25**: mp 161-163 °C; ^1H NMR [300 MHz, $(CD_3)_2SO$] d 2.43 (s, 3H), 3.87 (m, 3H), 4.22 (t, 1H), 4.99 (m, 1H), 7.51 (d, 1H), 7.77 (m, 2H), 8.26 (s, 1H), 8.97 (d, 1H), 10.35 (broad s, 1H); IR (mull) 3259, 3226, 3044, 1752 cm^{-1}; MS(ES) *m/z* 336 ($M+H^+$), 358 ($M+Na^+$). Anal. calcd for $C_{14}H_{14}FN_5O_2S$: C, 50.14; H, 4.21; N, 20.88. Found: C, 50.18; H, 4.26; N, 20.94.

EXAMPLE 23: (*S*)-N-[[3-[4-[1-[1,2,4]Triazolyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (25).



277.27 **26**

335.36 $C_{14}H_{14}FN_5O_2S$ **25**

A stirred mixture of **26**[10,12] (0.26 g, 0.938 mmol), ethyl dithioacetate (0.12 g, 0.998 mmol), sodium fluoride (0.040 g, 0.953 mmol) and absolute EtOH (10 mL), under nitrogen, was treated during 5 min with a solution of 0.97 M KOH (1.03 mL) in EtOH and kept at ambient temperature for 2 h. It was then diluted with CH_2CL_2 (75mL), washed with water, 1M $KHSO_4$, water and brine and evaporated. The residue was flash chromatographed on silica gel with 5% MeOH-$CHCl_3$ and the product was crystallized from MeOH to give 0.118 g, mp 164-165°C (dec) and 0.026 g, mp 162-163°C (dec) of **25**.

EXAMPLE 24: (*S*)-N-[[3-[1-(Hydroxyacetyl)-5-indolinyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (28).

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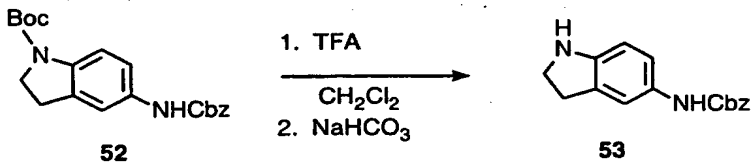
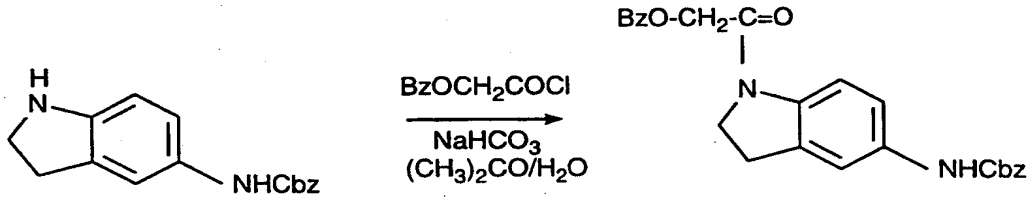
1.



52 53

A stirred, ice cold solution of **52**[13,14] (8.80 g, 0.0240 mol) in CH_2Cl_2 (25 mL) was treated during 20 min with a solution of trifluoroacetic acid (25 mL) in CH_2Cl_2 (10 mL). The mixture was kept in the ice bath for 2 h 15 min and concentrated under reduced pressure. A solution of the residue in CH_2Cl_2 was washed with saturated $NaHCO_3$ and dilute NaCl, dried (Na_2SO_4) and concentrated. The residue was used in the next reaction without further purification. A sample of this material (**53**) had: ^1H NMR (300 MHz, $CDCl_3$) d 3.00 (t, 2H), 3.54 (t, 2H), 3.85 (broad s, 1H), 5.17 (s, 2H), 6.59 (d, 1H), 6.66 (broad s, 1H), 6.91 (d, 1H), 7.23 (s, 1H), 7.36 (m, 5H); MS *m/z* 269 ($M+H^+$).

2.



268.22
$C_{16}H_{16}N_2O_2$
53

416.48
$C_{25}H_{24}N_2O_4$
54

An ice cold, stirred mixture of **53** (crude product from the previous reaction), acetone (200 mL), saturated $NaHCO_3$ (200 mL) and water (30 mL) was treated, dropwise during 20 min, with a solution of benzyloxyacetyl chloride (4.70 mL, 0.030 mol) in acetone (55 mL), warmed slowly to ambient temperature and kept for 18 h. Additional benzyloxytacetyl chloride (1.0 mL) in acetone 35 mL) was added dropwise and the mixture was kept at ambient temperature for an additional 3 h and diluted with EtOAc and water. A solid was collected by filtration and dried to give 4.00 g of crude product. The EtOAc solution was dried (Na_2SO_4) and concentrated to give 5.36 g of additional crude product. Crystallization of the product from EtOAc gave a total of 6.35 g of **54**[14], mp 157-159.5°C. The analytical sample had: mp 158-159.5°C; ^1H NMR (300 MHz, $CDCl_3$) δ 3,16 (t,2H), 4.01(t,2H), 4.21 (s, 2H), 4.69 (s,

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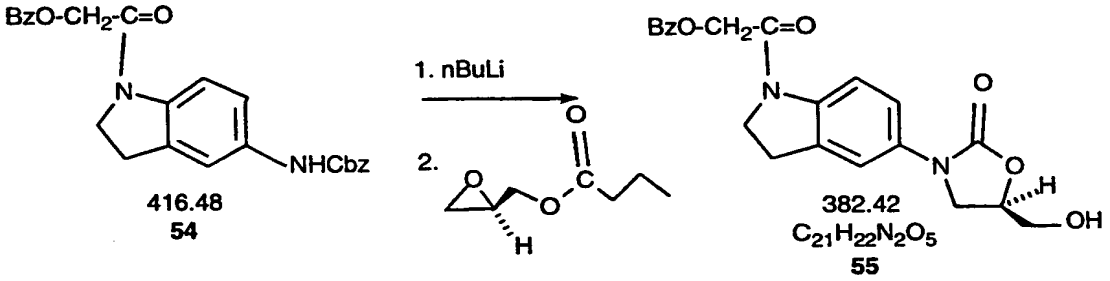
2H), 5.19 (s, 2H), 6.67 (s, 1H), 6.97 (d, 1H), 7.36 (m, 10H), 7.50 (braod s, 1H), 8.15 (d, 1H); MS(EI) *m/z* (relative intensity) 416 (M^+, 9), 310 (8), 202 (10), 133 (8), 92 (8), 91 (99), 79 (7), 77 (9), 65 (12), 51 (6); IR (mull) 2381, 1722, 1659, 1608, 1558 cm^{-1}. Anal. calcd for $C_{25}H_{24}N_2O_4$: C, 72.10; H, 5.81; N, 6.73. Found: C, 72.05; H, 5.86; N, 6.68.

3.

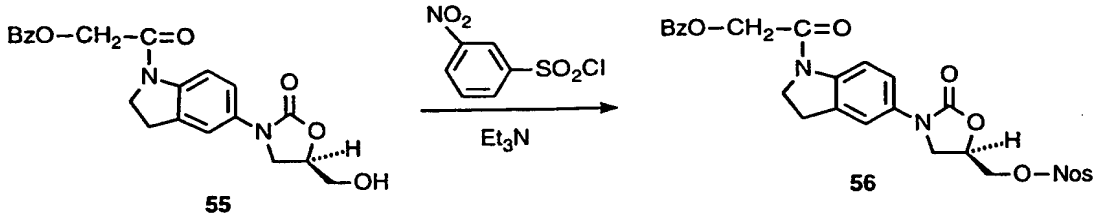


416.48
54

382.42
$C_{21}H_{22}N_2O_5$
55

A stirred suspension of **54** (1.16 g, 2.78 mmol) in THF (42 mL) was cooled, under nitrogen, to -78°C and treated, dropwise, during 5 min with 1.6 M n-BuLi in hexane (1.83 mL). It was kept at -78°C for 50 min, treated, dropwise, during 5 min with a solution of (R)-(-)-glycidyl butyrate (0.500 g, 3.47 mmol) in THF (2 mL), allowed to warm to ambient temperature during 3 h and kpet for 18 h. It was then diluted with EtOAc, washed with saturated NH_4Cl, water and brine, dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel with 3% MeOH-0.2% NH_4OH-$CHCl_3$ gave 0.60 g (56%) of **55**[14]: ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 3.14 (t, 2H), 3.59 (m, 2H), 3.79 (d,d, 1H), 4.03 (m, 3H), 4.29 (s, 2H), 4.58 (s, 2H), 4.65 (m, 1H), 5.20 (t, 1H), 7.31 (m, 6H), 7.55 (s, 1H), 8.03 (d, 1H); MS(ES) *m/z* 383 ($M+H^+$), 405 ($M+Na^+$).

4.



55

56

An ice cold, stirred mixture of **55** (0.60 g, 1.57 mmol), triethylamine (2.2 mL), and CH_2Cl_2 (12 mL), under nitrogen, was treated with 3-nitrobenzenesulfonyl chloride (0.44 g, 1.99 mmol) and kept in the ice bath for 30 min and at ambient temperature for 60 min. It was then diluted with CH_2Cl_2, washed with water and brine, dried

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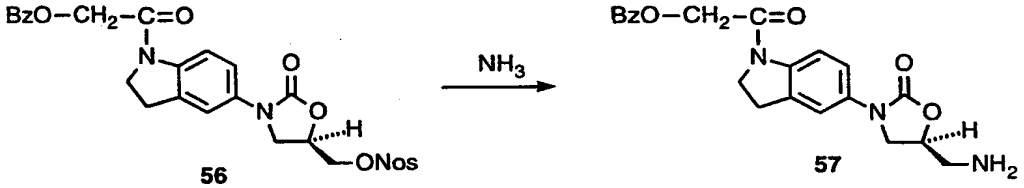
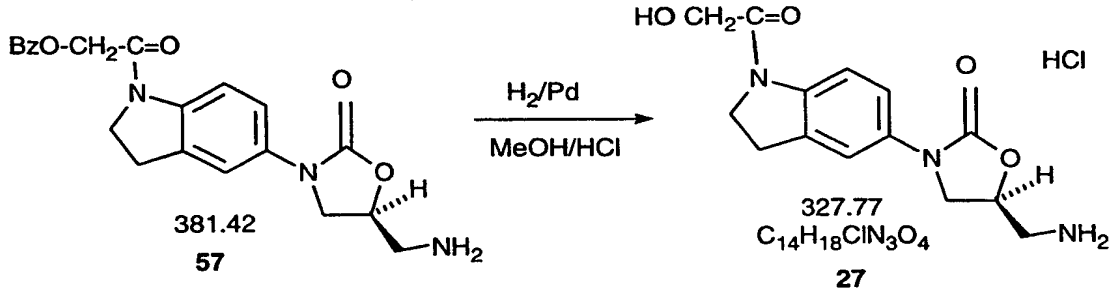
(Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with 15% CH_3CN-CH_2Cl_2 gave 0.70 g of **56**: ^1H NMR (300 MHz, $CDCl_3$) d 3.19 (t, J = 8.3 Hz, 2H), 3.88 (d,d, 1H), 4.04 (t, J = 8.4 Hz, 2H), 4.14 (t, 1H), 4.23 (s, 2H), 4.42 (m, 2H), 4.70 (s, 2H), 4.84 (m, 1H), 6.97 (m, 1H), 7.34 (m, 5H), 7.58 (s, 1H), 7.81 (t, 1H), 8.22 (m, 2H), 8.53 (m, 1H), 8.73 (m, 1H); MS(ES) m/z 568 ($M+H^+$), 590 ($M+Na^+$).

5.



A stirred mixture of **56** (crude product from 0.00314 mol of **55**), acetonitride (70 mL), isopropanol (70 mL) and 29% ammonium hydroxide (70 mL) was warmed at 40-44 °C for 7h and kept at ambient temperature for 18 h. It was concentrated in vacuo to an aqueous residue with was extracted with CH_2Cl_2. The extract was washed with water and brine, dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with 8% MeOH-0.5% NH_4OH-$CHCl_3$ gave 1.05 g of **57**: ^1H NMR [300 MHz, $(CD_3)_2SO$] d 2.78 (m, 2H), 3.13 (t, 2H), 3.82 (d,d, 1H), 4.01 (m, 3H), 4.29 (s, 2H), 4.58 (s, 2H), 4.58 (m, 1H), 7.31 (m, 6H), 7.54 (broad s, 1H), 8.03 (d, 1H); MS(ES) m/z 382 ($M+H^+$), 404 ($M+Na^+$).

6.



A mixture of **57** (0.46 g, 1.21 mmol), MeOH (150 mL), 1 M HCl (1.2 mL) and 5% palladium-on-carbon catalyst (250 mg) was hydrogenated at an initial pressure of 49 psi for 5 h. Additional 1M HCl (0.5 mL) and catalyst (100 mg) were added and hydrogenation was continued for 18 h. The catalyst was removed by filtration and

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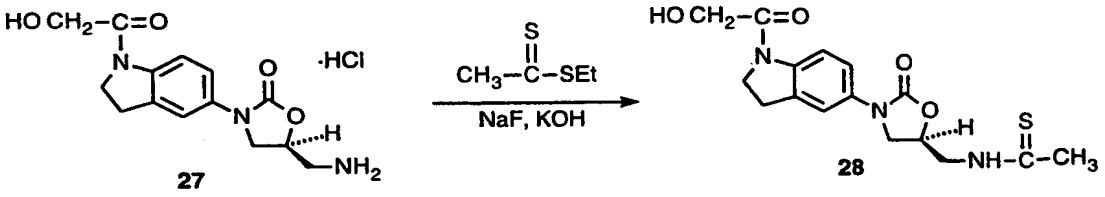
the filtrate was concentrated to give 0.34 g of **27**: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 3.15 (t, 2H), 3.22 (broad s, 2H), 3.84 (d,d, 1H), 4.00 (t, 2H), 4.15 (s, 2H), 4.15 (m, 1H), 4.92 (m, 1H), 7.24 (q, 1H), 7.50 (d, 1H), 8.03 (d, 1H), 8.37 (broad s, 3H); MS(ES) *m/z* 2.92 ($M+H^+$).

7.

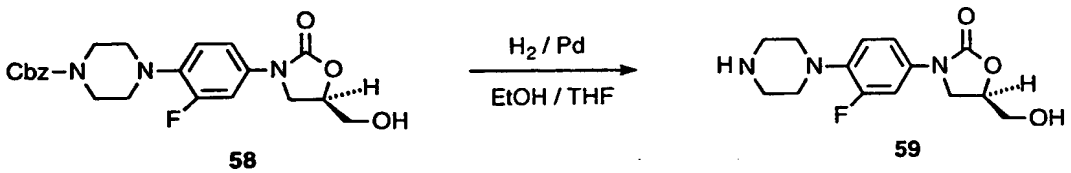


27 28

A suspension of **27** (0.10 g, 0.34 mmol) in a mixture of EtOH (15 mL) and 0.97 M KOH (0.7 mL) was added, under nitrogen to a stirred mixture of ethyl dithioacetate (0.0412 g, 0.343 mmol) and sodium fluoride (0.0137 g, 0.326 mmol) in EtOH (5 mL) and the mixture was kept at ambient temperature for 2h 15 min. Additional 0.97 M KOH (0.2 mL), sodium iodide (6 mg) and ethyl dithioacetate (20 mg) were added and the mixture was stirred for 2 h, mixed with CH_2Cl_2 (150 mL), washed with water, 1M $KHSO_4$ and brine, dried (Na_2SO_4) and concentrated. The residue was crystallized from acetone to give 0.0404 g of **28**: mp 175-176 °C (dec); MS (FAB) *m/z* 350 ($M+H^+$), 349 (M^+), 331, 316, 205, 73; HR MS (FAB) calcd for $C_{16}H_{20}N_3O_4S$ ($M+H^+$) 350.1174, found 350.1183; ^{1}H NMR [300 MHz, $(CD_3)_2SO$] d 2.42 (s, 3H), 3.14 (t, 2H), 3.79 (d,d, 1H), 3.89 (t, 2H), 4.00 (t, 2H), 4.12 (m, 3H), 4.83 (t, 1H), 4.90 (m, 1H), 7.25 (d, 1H), 7.50 (s, 1H), 8.03 (d, 1H), 10.35 (s, 1H); IR (DRIFT) 3255, 3223, 3068, 1747, 1639, 1614 cm^{-1}.

EXAMPLE 25: (*S*)-N-[[3-[3-Fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (30).

1.



58 59

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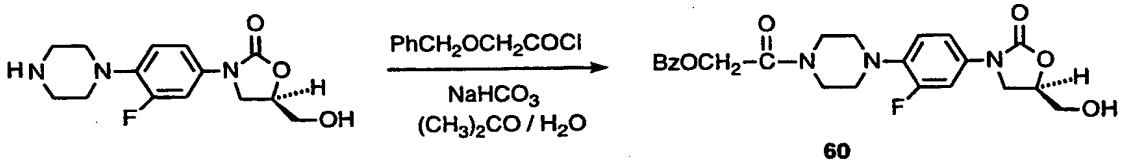
A mixture of **58**[15] (3.00 g, 7.00 mmol), THF (60 mL), absolute EtOH (100 mL) and 10% palladium-on-carbon catalyst (415 mg) was hydrogenated at an initial pressure of 58 psi for 2 h 50 min. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give 2.67 g of **59** which was used without further purification in the next reaction: ^{1}H NMR (300 MHz, $CDCl_3$) d 2.16 (broad s), 3.02 (m, 8H), 3.73 (d,d, J = 3.9, 12.6 Hz, 1H), 3.96 (m, 3H), 4.72 (m, 1H), 6.92 (t, J = 9.2 Hz, 1H), 7.11 (m, 1H), 7.43 (d,d, J = 2.6, 14.3 Hz, 1H); MS(ES) m/z 296 ($M+H^+$).

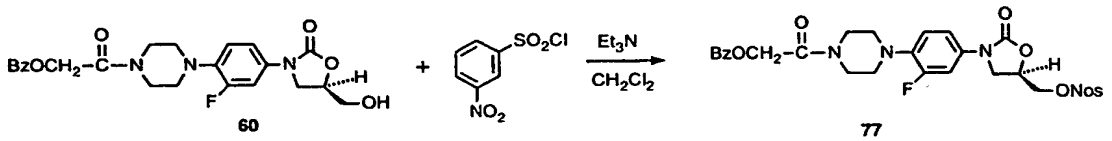
2.



59 **60**

A stirred, ice cold mixture of **59** (2.67 g from the previous reaction), acetone (190 mL) and saturated $NaHCO_3$ (70 mL) was treated, dropwise during 2-3 min with a solution of benzyloxyacetyl chloride (1.34 mL, 8.61 mmol) in acetone (25 mL), kept in the ice bath for 1 h and diluted with EtOAc. The aqueous layer was extracted with EtOAc and the combined organic solution was washed with dilute NaCl, dried and concentrated. Chromatography of the residue on silica gel with 30% acetone-CH_2Cl_2 gave 2.64 g of **60**: ^{1}H NMR (300 MHz, $CDCl_3$) d 2.28 (broad s, 1H), 3.00 (m, 4H), 3.66 (m, 2H), 3.77 (m, 3H), 3.96 (m, 3H), 4.22 (s, 2H), 4.61 (s, 2H), 4.74 (m, 1H), 6.88 (t, J = 9.2 Hz, 1H), 7.12 (m, 1H), 7.35 (s, 5H), 7.46 (d,d, J = 2.6, 14.2 Hz, 1H); IR (mull) 3406, 1748, 1647 cm^{-1}; HRMS(EI) calcd for $C_{23}H_{26}FN_3O_5$ (M^+) 443.1856, found 443.1842.

3.



60 **77**

A stirred, ice cold mixture of **60** (2.64 g, 6.00 mmol) and triethylamine (1.14 mL, 8.16 mmol) in CH_2Cl_2 (200 mL), under nitrogen, was treated with 3-nitrobenzenesulfonyl chloride (1.78 g, 8.04 mmol), warmed to ambient temperature and kept for 5 h 20 min. Additional 3-nitrobenzenesulfonyl chlroide (180 mg) and triethylamine (0.20 mL) were added and the mixture was kept at ambient

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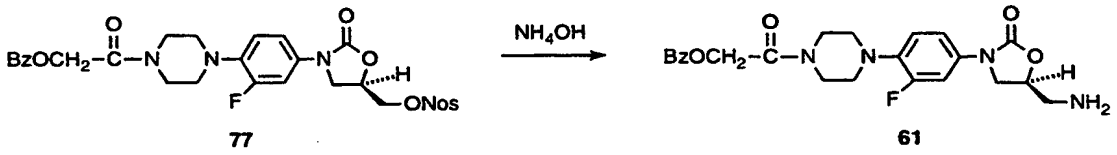
temperature for 18 h, diluted with CH_2Cl_2 and washed with water and dilute NaCl, dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with 40-60% acetone-hexane gave 3.36 g of **77**: ^{1}H NMR (300 MHz, $CDCl_3$) d 3.02 (broad s, 4H), 3.66 (broad s, 2H), 3.78 (broad s, 2H), 3.87 (d,d, J = 5.9, 9.1 Hz, 1H), 4.09 (t, J = 9.2 Hz, 1H), 4.22 (s, 2H), 4.41 (m, 2H), 4.61 (s, 2H), 4.84 (m, 1H), 6.88 (t, J = 9.1 Hz, 1H), 7.02 (m, 1H), 7.35 (m, 6H), 7.82 (t, J = 8.0 Hz, 1H), 8.23 (m, 1H), 8.53 (m, 1H), 8.73 (m, 1H); MS(ES) m/z 629 ($M+H^+$).

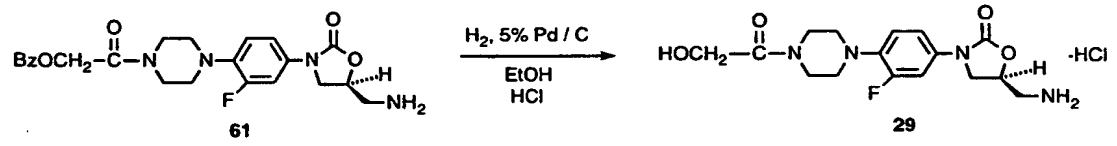
4.



77 61

A solution of **77** (3.36 g, 5.34 mmol) in a mixture of acetonitrile (90 mL), isopropanol (90 mL) and concentrated ammonium hydroxide (90 mL) was warmed at 40-45 °C for 18 h, treated with additional ammonium hydroxide (30 mL), warmed at 40-45 °C for 8 h, treated with additional ammonium hydroxide (25 mL) and warmed at 45 °C for 18 h. It was then mixed with water and extracted with CH_2Cl_2. The extract was washed with dilute NaCl, dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with 5% MeOH-0.5% NH_4OH-$CHCl_3$ gave 2.44 g of **61**: ^{1}H NMR (300 MHz, $CDCl_3$) d 1.50 (broad s), 3.04 (m, 6H), 3.65 (broad s, 2H), 3.81 (m, 3H), 3.99 (t, 1H), 4.21 (s, 2H), 4.61 (s, 2H), 4.66 (m, 1H), 6.88 (t, 1H), 7.12 (m, 1H), 7.33 (m, 5H), 7.47 (d,d, 1H); MS(ES) m/z 443 ($M+H^+$).

5.



61 29

A solution of **61** (1.45 g, 3.3 mmol) and 1.0 N HCl (3.65 mL) in 95% EtOH (150 mL) was treated with 5% palladium-on-carbon catalyst (500 mg) and hydrogenated at an initial pressure of 54 psi for 20 h 15 min. Additional 1.0 N HCl (0.5 mL) and catalyst (100 mg) were added and hydrogenation was continued for 20 h 30 min at an initial pressure of 60 psi. The reaction was compete by TLC; it was neutralized with concentrated NH_4OH, filtered and concentrated in vacuo to give 1.18 g of **29**: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] d 2.94 (broad s, 4H), 3.19 (m, 2H), 3.48 (broad s, 2H),

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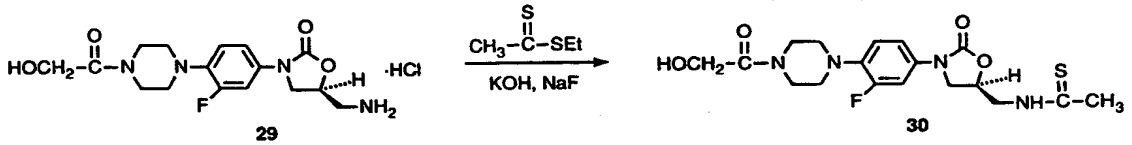
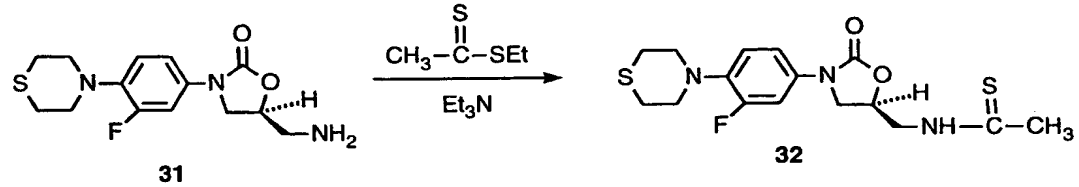
3.60 (broad s, 2H), 3.84 (m, 1H), 4.14 (m, 3H), 4.66 (broad s, 1H), 4.93 (m, 1H), 7.07 (t, 1H), 7.16 (d,d, 1H), 7.48 (d,d, 1H), 8.04 (broad s); IR (mull) 3420, 3099, 3040, 3008, 1755, 1641 cm^{-1}; MS(ES) *m/z* 353 ($M+H^+$). Anal. calcd for $C_{16}H_{22}ClFN_4O_4$: C, 49.42; H, 5.70; Cl, 9.12; N, 14.41. Found: C, 48.16; H, 5.82; Cl, 10.00; N, 14.28.

6.



A stirred mixture of ethyl dithioacetate (180 mL, 1.56 mmol), sodium fluoride (72 mg, 1.7 mmol), **29** (500 mg, 1.29 mmol) and EtOH (70 mL) under nitrogen, was treated with 0.97M KOH (1.46 mL, 1.42 mmol) and the resulting solution was kept at ambient temperature for 3 h 35 min, diluted with $CHCl_3$, washed with water and dilute NaCl, dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with 5% MeOH-0.5% NH_4OH-$CHCl_3$ and crystallization of the resulting product from absolute EtOH gave 0.238 mg (44.9%) **30**: mp 163-165 °C; ^1H NMR (300 MHz, $CDCl_3$) d 2.60 (s, 3H), 3.06 (m, 4H), 3.45 (m, 2H), 3.61 (m, 1H), 3.82 (m, 3H), 4.07 (m, 2H), 4.25 (m, 3H), 4.97 (m, 1H), 6.91 (t, 1H), 7.07 (m, 1H), 7.45 (d,d, 1H), 7.91 (broad s, 1H); MS(FAB) *m/z* (relative intensity) 411 ($M+H^+$, 100), 410 (M^+, 66.5), 266 (3.1); IR 3292, 1733, 1653 cm^{-1}. Anal. calcd for $C_{18}H_{23}FN_4O_4S$: C, 52.67; H, 5.65; N, 13.65. Found: C, 52.76; H, 5.58; N, 13.64.

EXAMPLE 26: **(*S*)-N-[[3-[3-Fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thio-acetamide (32).**



An ice cold, stirred mixture of **31** (0.38 g, 0.0012 mol) and triethylamine (0.38 mL, 0.0027 mol) in THF (12 mL), under nitrogen, was treated with ethyl dithioacetate (0.16 mL, 0.0014 mol) and then kept at ambient temperature for 24.5 h and concentrated in vacuo. A solution of the residue in CH_2Cl_2 was washed with

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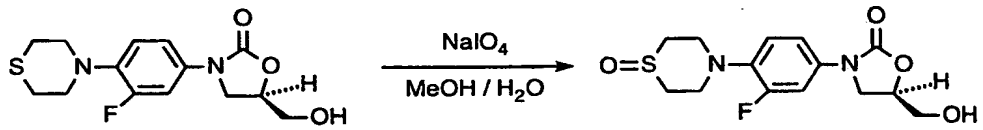
saturated $NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated. Crystallization of the residue from EtOAc-hexane gave 0.355 g of **32**: mp 155-156 °C; MS(ES) *m/z* 370 ($M+H^+$), 392 ($M+Na^+$); IR (DRIFT) 3206, 3042, 1759, 1738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) d 2.60 (s, 3H), 2.95 (s, 4H), 3.43 (m, 4H), 3.82 (d, d, 1H), 4.08 (m, 2H), 4.27 (m, 1H), 4.98 (m, 1H), 7.06 (m, 1H), 7.33 (broad s, 1H), 7.51 (d, 1H), 8.03 (broad s, 1H). Anal. calcd for $C_{16}H_{20}FN_3O_2S_2$: C, 52.01; H, 5.46; N, 11.37. Found: C, 51.86; H, 5.43; N, 11.20.

EXAMPLE 27: **(*S*)-N-[[3-[3-Fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thio-acetamide, thiomorpholine S-oxide (34).**

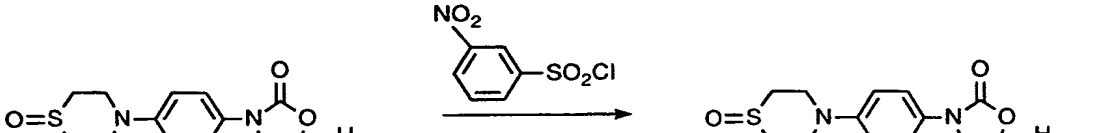
1.



62 **63**

An ice cold, stirred mixture of sodium metaperiodate (1.08 g, 5.05 mmol) and water (12 mL), under nitrogen, was treated with **62**[16] (1.5 g, 4.8 mmol) and MeOH (17 mL) and kept at 6 °C for 18 h and at 4 °C for 3 h. It was then treated with additional sodium metaperiodate (0.1 g), kept at 4°C for 3 h and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and concntrated to give 1.4 g of **63**: ^1H NMR [300 MHz, $(CD_3)_2SO$] d 2.84 (m, 2H), 3.01 (m, 2H), 3.16 (m, 2H), 3.50 (m, 3H), 3.65 (m, 1H), 3.77 (d,d, 1H), 4.03 (t, 1H), 4.66 (m, 1H), 5.18 (t, 1H), 7.16 (m, 2H), 7.52 (m, 1H); MS(ES) *m/z* 329 ($M+H^+$), 351 ($M+Na^+$).

2.



63 **78**

An ice cold, stirred mixture of **63** (1.27 g, 3.87 mmol) and triethylamine (0.732 mL, 5.25 mmol) in CH_2Cl_2 (130 mL), under nitrogen, was treated with *m*-nitrobenzenesulfonyl chloride (1.15 g, 5.19 mmol) and kept at ambient temperature for about 24 h. It was diluted with CH_2Cl_2, washed with water and brine, dried (Na_2SO_4) and concentrated to give **78** which was used in the next reaction without

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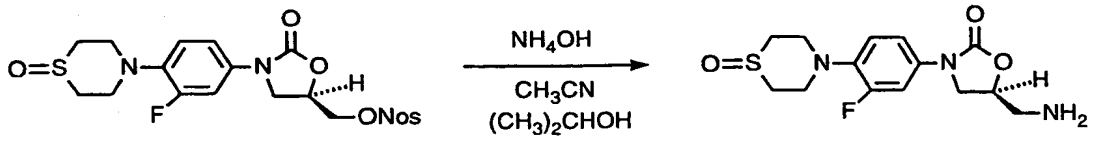
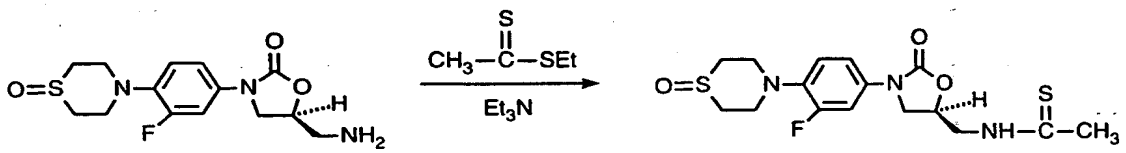
purification.

3. 

78 33

A stirred mixture of the product (**78**) from the previous reaction, acetonitrile (70 mL) and isopropanol (70 mL) was treated with concentrated ammonium hydroxide (70 mL, 29.9% NH_3) and kept at 40 °C for 2 h, at ambient temperature for 18 h and at 40-45 °C for 4 h; it was concentrated to about 50 mL, diluted with water and extracted with CH_2Cl_2. The extracts were washed with water and brine, dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel with 5% MeOH-$CHCl_3$ gave 0.58 g of **33**: MS(ES) *m/z* 328 ($M+H^+$), 350 ($M+Na^+$); ^1H NMR [300 MHz, $(CD_3)_2SO$] d 2.81 (m, 4H), 3.01 (m, 2H), 3.16 (m, 2H), 3.30 (broad s), 3.49 (m, 2H), 3.80 (d,d, 1H), 4.01 (t, 1H), 4.58 (m, 1H), 7.19 (m, 2H), 7.51 (m, 1H).

4. 

33 34

A stirred suspension of **33** (3.7 g, 0.011 mol) and triethylamine (3.5 mL, 0.025 mol) in THF (120 mL) was cooled, in an ice bath, under nitrogen, treated, dropwise during 2 min, with a solution of ethyl dithioacetate (1.47 mL, 0.0128 mol) in THF (2 mL) and kept at ambient temperature for 22 h. The resulting solution was concentrated and the residue crystallized from acetonitrile to give 3.61 g of **34**: mp 176-177 °C ; ^1H NMR [300 MHz, $(CD_3)_2SO$] d 2.42 (s, 3H), 2.85 (m, 2H), 3.01 (m, 2H), 3.18 (m, 3H), 3.50 (m, 2H), 3.78 (d,d, 1H), 3.89 (broad s, 2H), 4.12 (t, 1H), 4.92 (m, 1H), 7.18 (m, 2H), 7.49 (m, 1H), 10.33 (s, 1H); IR (DRIFT) 3186, 3102, 1741 cm^{-1}; MS(ES) *m/z* 386 ($M+H^+$), 408 ($M+Na^+$). Anal. calcd for $C_{16}H_{20}FN_3O_3S_2 \cdot 0.5 H_2O$: C, 48.71; H, 5.37; N, 10.65; S, 16.26; H_2O, 2.38. Found: C, 48.75; H, 5.17; N, 10.72; S, 16.07; H_2O, 1.72.

EXAMPLE 28: **(*S*)-N-[[3-[3-Fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-**

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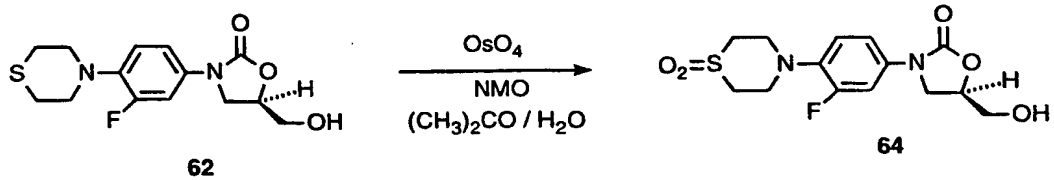
oxazolidinyl]methyl]thio-acetamide, thiomorpholine S, S-dioxide (36).

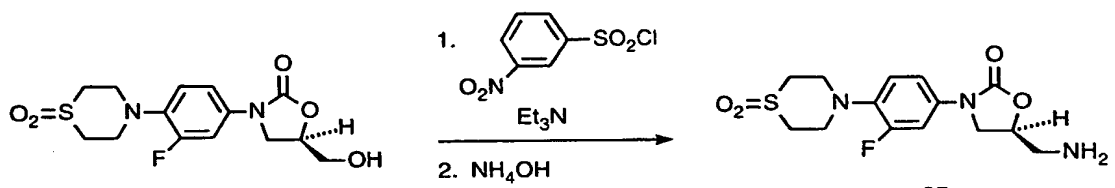
1.



62 64

A stirred mixture of **62**[16] (0.399 g, 0.00128 mol) in 25% water/acetone (12 mL), under nitrogen was treated with N-methylmorpholine, N-oxide (0.45 g, 0.00384 mol) and 0.1 mL of a 2.5 wt% solution of osmium tetroxide in *tert*-butanol. It was kept at ambient temperature for 18 h, mixed with saturated $NaHSO_3$ (50 mL) and extracted with CH_2Cl_2. The extract was washed with saturated $NaHSO_3$ and brine, dried (Na_2SO_4) and concentrated. The residue was mixed with 3.5% MeOH-CH_2Cl_2 and filtered; the solid was dissolved in 15% MeOH-CH_2Cl_2 and concentrated to give 0.29 g of **64**. The filtrate was chromatographed on silica gel with 3.5% MeOH-CH_2Cl_2 to give 0.1 of additional **64**: MS(ES) *m/z* 345 ($M+H^+$), 367 ($M+Na^+$); ^1H NMR [300 MHz, $(CD_3)_2SO$] d 3.26 (m, 4H), 3.44 (m, 4H), 3.60 (m, 2H), 3.80 (d,d, 1H), 4.05 (t, 1H), 4.69 (m, 1H), 7.22 (m, 2H), 7.54 (d, 1H).

2.



64 35

A stirred mixture of **64** (0.39 g, 0.00113 mol) and triethylamine (0.214 mL, 0.00154 mol) in CH_2Cl_2 (37 mL) was cooled, under nitrogen, in an ice bath and treated, portionwise during 5 min, with 3-nitrobenzenesulfonyl chloride (0.335 g, 0.00151 mol). The mixture was kept in the ice bath for 20 min and at ambient temperature for 18 h and concentrated in vacuo. A stirred solution of the residue in 2-propanol (25 mL) and acetonitrile (25 mL), under nitrogen, was treated with 30% NH_4OH (25 mL), warmed at 50-55 °C for 6 h and kept at ambient temperature for 48 h. It was concentrated to remove the organic solvents, diluted with water and extracted with CH_2Cl_2. The extract was washed with water and brine, dried ($MgSO_4$) and

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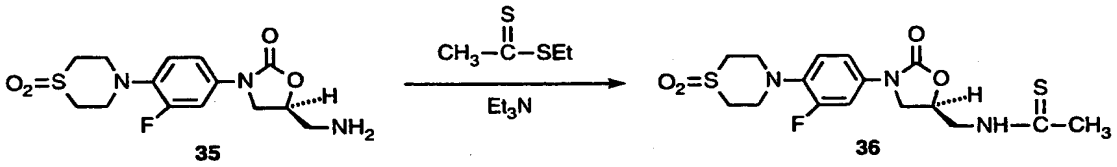
concentrated. Flash chromatography of the residue on silica gel with 6% MeOH-0.4% NH_4OH-$CHCl_3$ gave 0.29 g of **35**: ^1H NMR [300 MHz, $(CD_3)_2SO$] d 1.59 (broad s, 2H), 2.78 (m, 2H), 3.24 (m, 4H), 3.43 (m, 4H), 3.81 (d,d, 1H), 4.01 (t, 1H), 4.57 (m, 1H), 7.18 (m, 2H), 7.52 (m, 1H); MS(ES) *m/z* 344 ($M+H^+$), 366 ($M+Na^+$).

3.

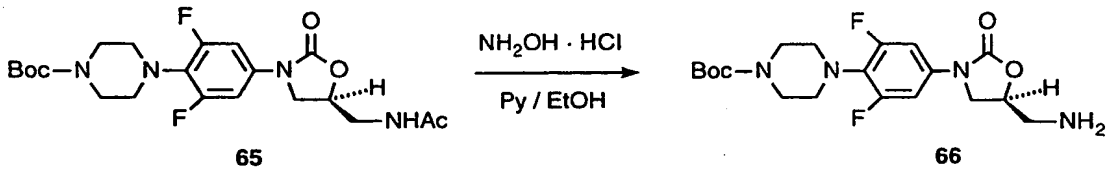


35 **36**

A stirred, ice cold suspension of **35** (0.28 g, 0.85 mmol) in a mixture of Et_3N (0.26 mL, 1.9 mmmol) and THF (10 mL) was treated with ethyl dithioacetate (0.11 mL, about 6 drops) and kept in the ice bath for 20 min and then at ambient temperature; the reaction was followed by TLC. After 20 h there was still a suspension and only partial reaction; additional THF (10 mL) and ethyl dithioacetate (3 drops) were added. After an additional 48 h the reaction was still incomplete; the suspension was treated with CH_2Cl_2 (10 mL) and kept for 72 h. At this time almost complete solution and an almost complete conversion to product had been obtained. An additional drop of ethyl dithioacetate was added and the mixture was kept at ambient temperature for 5 d and concentrated in vacuo. The residue was mixed with EtOAc, washed with saturated $NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated. Crystallization of the residue from MeOH-EtOAc gave 0.209 g of **36**: mp 197-198 °C; ^1H NMR [300 MHz, $(CD_3)_2SO$] d 2.42 (s, 3H), 3.24 (m, 4H), 3.43 (m, 4H), 3.78 (d,d, 1H), 3.88 (m, 2H), 4.12 (t, 1H), 4.92 (m, 1H), 7.18 (m, 2H), 7.50 (m, 1H), 10.37 (broad s, 1H); IR (mull) 3300, 3267, 1743 cm^{-1}; MS(ES) *m/z* 424 ($M+Na^+$). Anal. calcd for $C_{16}H_{20}FN_3O_4S_2$: C, 47.87; H, 5.02; N, 10.47. Found: C, 47.84; H, 5.23; N, 10.28.

EXAMPLE 29: **(*S*)-N-[[3-[3,5-Difluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (38).**

1.



65 **66**

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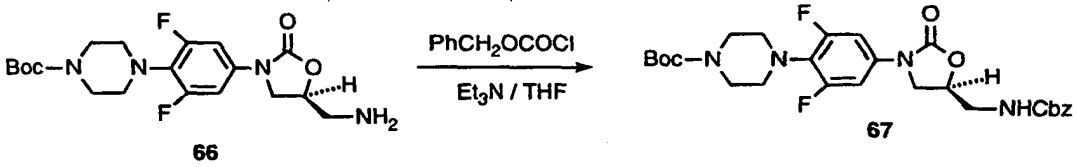
A stirred mixture of **65**[17,18] (1.8 g, 0.00396 mol), pyridine (30 mL) and absolute EtOH (3 mL), under nitrogen, was treated with hydroxylamine hydrochloride (1.44 g, 0.0207 mol), warmed to the reflux temperature during 2 h, refluxed for 3.5 h, kept at ambient temperature for 18 h and at reflux for 4 h. It was concentrated in vacuo and the residue was mixed with water, adjusted to pH 11 with saturated $NaHCO_3$ and extracted with Et_2O. The extracts were washed with brine, dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with 5% MeOH-0.35% NH_4OH-$CHCl_3$ gave 0.75 g of recovered **65** and 0.72 g of **66**: ^1H NMR [300 MHz, $(CD_3)_2SO$] d 1.40 (s, 9H), 1.72 (broad s, 2H), 2.78 (m, 2H), 2.97 (m, 4H), 3.40 (m, 4H), 3.80 (d,d, 1H), 4.00 (t, 1H), 4.59 (m, 1H), 7.27 (d, 2H); MS(ES) *m/z* 413 ($M+H^+$), 435 ($M+Na^+$).

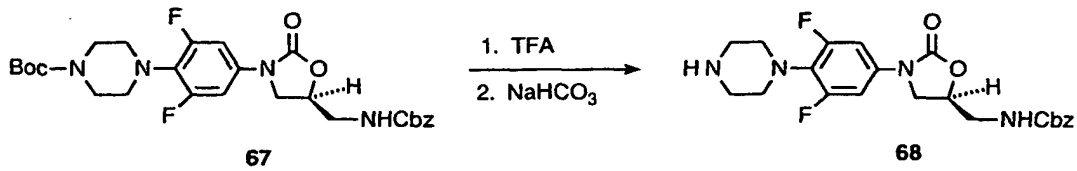
2.



66 **67**

An ice cold, stirred mixture of **66** (0.75 g, 0.0018 mol) and triethylamine (0.315 mL, 0.00225 mol) in THF (12 mL), under nitrogen, was treated, dropwise with benzyl chloroformate (0.29 mL, 0.0020 mol), kept in the ice bath for 15 min and at ambient temperature for 2 h and concentrated in vacuo. The residue was mixed with CH_2Cl_2 and washed with saturated $NaHCO_3$, water and brine, dried (Na_2SO_4) and concentrated. This residue was mixed with Et_2O and filtered to give 0.939 g of **67**: mp 116-118 °C; ^1H NMR (300 MHz, $CDCl_3$) d 1.48 (s, 9H), 3.08 (m, 4H), 3.53 (m, 4H), 3.60 (m, 2H), 3.73 (m, 1H), 3.96 (t, 1H), 4.76 (m, 1H), 5.10 (s, 2H), 5.21 (m, 1H),7.07 (d, 2H), 7.31 (s, 5H); MS(ES) *m/z* 547 ($M+H^+$), 569 ($M+Na^+$).

3.



67 **68**

Compound **67** (0.805 g, 0.00147 mol) was added with stirring, portionwise during 5 min, under nitrogen, to ice cold trifluoroacetic acid (9 mL). The resulting solution was kept in the ice bath for 1 h and then concentrated under a stream of nitrogen.

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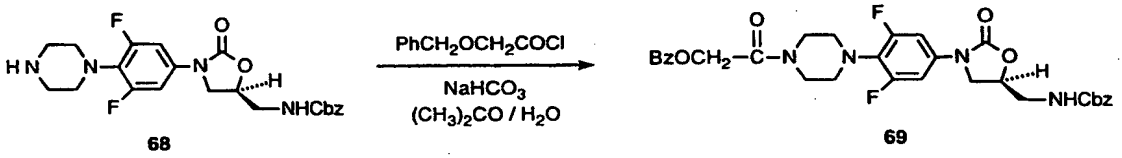
The residue was mixed with ice and saturated $NaHCO_3$ and extracted with CH_2Cl_2; the extract was washed with water and brine, dried (Na_2SO_4) and concentrated to give 0.63 g of product. The combined aqueous layer was reextracted with EtOAc; the extracts were washed with water and brine, dried (Na_2SO_4) and concntrated to give additional product. The combined product amounted to 0.68 g of **68** which was used in the next reaction without further purification.

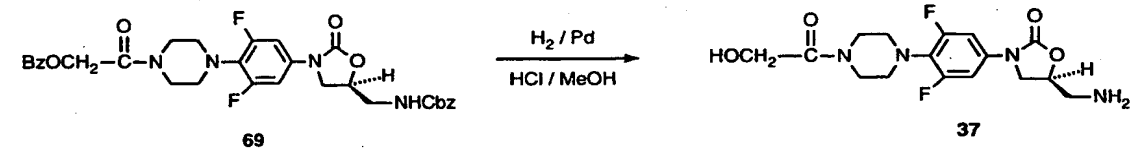
4.



68 69

An ice cold, stirred mixture of **68** (0.68 g, 0.00152 mol), saturated $NaHCO_3$ (15.2 mL) and acetone (40 mL), under nitrogen was treated, dropwise during 15 min, with a solution of benzyloxyacetyl chloride (0.29 mL, 0.0019 mol) in acetone (5 mL), kept at ambient temperature for 6 h, diluted with EtOAc and washed with water and brine. The extract was dried ($MgSO_4$) and concentrated in vacuo to give 0.72 g of **69**: MS(ES) *m/z* 395 ($M+H^+$), 617 ($M+Na^+$); ^1H NMR (300 MHz, $CDCl_3$) d 3.12 (m, 4H), 3.59 (m, 4H), 3.74 (m, 3H), 3.96 (t, 1H), 4.22 (s, 2H), 4.62 (s, 2H), 4.75 (broad s, 1H), 5.10 (s, 2H), 5.22 (m, 1H), 7.08 (d, 2H), 7.33 (m, 10H).

5.



69 37

A mixture of **69** (0.72 g, 0.0012 mol), MeOH and 5% palladium-on-carbon catalyst (0.4 g) was hydrogenated at an initial pressure of 45 psi for 4 h. By TLC (8% MeOH-0.5% NH_4OH-$CHCl_3$) the starting material had been reduced and two products formed. 1M Hydrochloric acid (1.34 mL) was added and hydrogenation was continued at an initial pressure of 40 psi for 21 h. By TLC only the more polar product remained. The catalyst was removed by filtration and the filtrate was concentrated to give 0.40 g of **37**: MS(ES) *m/z* 371 ($M+H^+$), 393 ($M+Na^+$); ^1H NMR [300 MHz, $(CD_3)_2SO$] d 3.02 (s, 4H), 3.20 (m, 2H), 3.43 (s, 2H), 3.56 (s, 2H), 3.84 (m,

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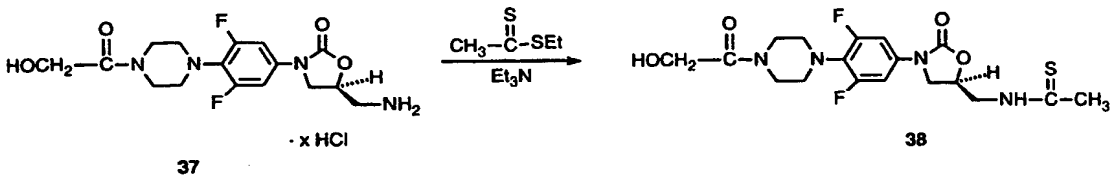
1H), 3.84 (broad s), 4.10 (s, 2H), 4.14 (t, 1H), 4.96 (m, 1H), 7.26 (d, 2H), 8.41 (broad s, 3H).

6.

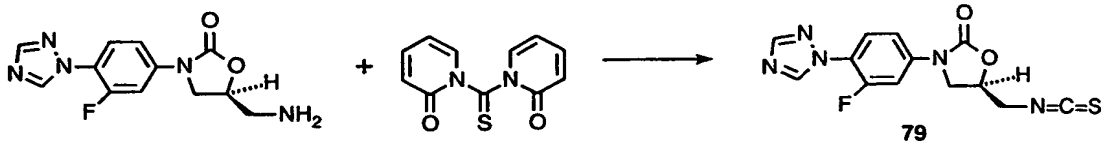


37 38

A stirred suspension of **37** (0.38 g) in a solution of Et_3N (0.31 mL) and THF (10 mL), under nitrogen, was treated with ethyl dithioacetate (0.13 mL, about 7 drops) and kept at ambient temperature for 7 d; the reaction was followed by TLC (8% MeOH-0.5% NH_4OH-$CHCl_3$). Additional ethyl dithioacetate (2 drops) was added after 24 h; after 30 h CH_2Cl_2 (10 mL) and ethyl dithioacetate (3 drops) were added; after 48 h additional triethylamine (0.3 mL) was added. The mixture was concentrated in vacuo and the residue was mixed with ice and saturated $NaHCO_3$ an extracted with CH_2Cl_2. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel with 2.5% MeOH-CH_2Cl_2 and the product was crystallized from MeOH to give 0.182 g of **38**: mp 110-111 °C (dec); MS(ES) *m/z* 429 ($M+H^+$), 451 ($M+Na^+$); HRMS (FAB) calcd for $C_{18}H_{23}F_2N_4O_4S$ ($M+H^+$) 429.1408, found 429.1415; IR (DRIFT) 1760, 1652, 1639 cm^{-1}; $[\alpha]^{24}_D$ 8° (MeOH).

EXAMPLE 30: **(*S*)-N-[[3-[4-[1-[1,2,4]Triazolyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea (44).**

1.



26 79

A solution of **26** (0.190 g, 0.685 mmol) in CH_2Cl_2 (20 mL) was added, dropwise during 20 min, under nitrogen, to an ice cold, stirred solution of 1,1¢-thiocarbonyldi-2(1H)-pyridone (0.193 g, 0.831 mmol) in CH_2Cl_2 (7 mL). The mixture was kept in the ice bath for 20 min and at ambient temperature for 2 h, diluted with CH_2Cl_2,

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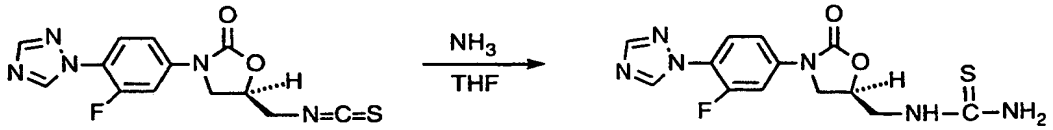
washed with water and brine, dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel with 10-15% CH_3CN-CH_2Cl_2 gave 0.11 g of **79** which was used in the next reaction without further purification: MS(ES) *m/z* 320 ($M+H^+$), 342 ($M+Na^+$).

2.

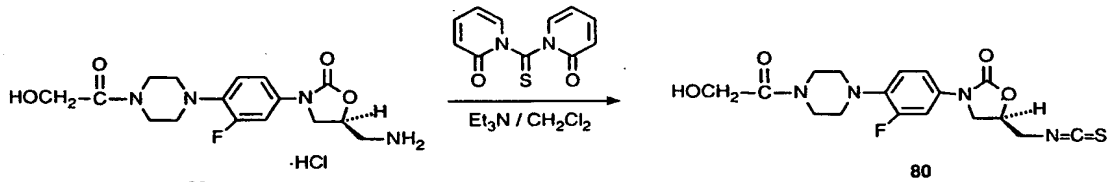


79 **44**

A stirred, ice cold solution of **79** (0.10 g, 0.31 mmol) in THF (15 mL) was treated with excess anhydrous ammonia and kept in the ice bath for 90 min. It was then evaporated under a stream of nitrogen to a volume of about 5 mL to give a solid which was collected by filtration and washed with cold THF to give 0.105 g of **44**: mp 214-215 °C; ^1H NMR [300 MHz, $(CD_3)_2SO$] d 3.82 (m, 3H), 4.18 (t, 1H), 4.89 (broad s, 1H), 7.20 (broad s, 2H), 7.50 (d, 1H), 7.79 (m, 2H), 7.93 (t, 1H), 8.26 (s, 1H), 8.97 (s, 1H); MS(ES) *m/z* 337 ($M+H^+$), 359 ($M+Na^+$). Anal. calcd for $C_{13}H_{13}FN_6O_2S$: C, 46.42; H, 3.90; N, 24.99. Found: C, 46.22; H, 3.98; N, 24.55.

EXAMPLE 31: **(*S*)-N-[[3-[3-Fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]-methyl]thiourea (45).**

1.



29 **80**

An ice cold, stirred solution of 1,1¢-thiocarbonyl-2(1H)-dipyridone (0.123 g, 0.530 mmol) in CH_2Cl_2 (5 mL), under nitrogen, was treated with a suspension of **29** (0.17 g, 0.4 mmol) in CH_2Cl_2 (20 mL) and then during 10 min with a solution of triethylamine (0.111 mL, 0.8 mmol) in CH_2Cl_2 (10 mL). It was kept in the ice bath for 30 min, at ambient temperature for 2 h and at < 0 °C for 18 h. It was then diluted with CH_2Cl_2, washed with water and brine, dried ($MgSO_4$) and concentrated. The residue (**80**) was used without further purification in the next

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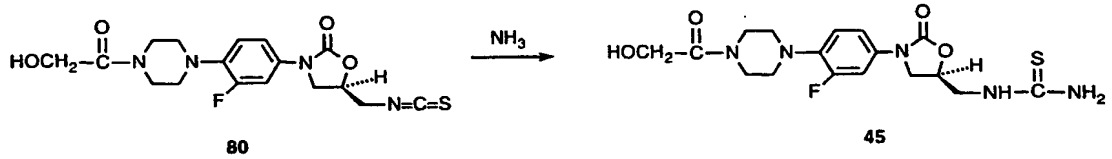
reaction. A sample of **80** that was purified by flash chromatography on silica gel with 10-20% acetonitrile-CH_2Cl_2 had: ^1H NMR (300 MHz, $CDCl_3$) d 1.60 (broad s), 3.07 (m, 4H), 3.45 (m, 2H), 3.85 (m, 4H), 3.97 (d,d, 1H), 4.16 (t, 1H), 4.21 (s, 2H), 4.82 (m, 1H), 6.95 (t, 1H), 7.13 (d,d, 1H), 7.47 (d,d, 1H); MS *m/z* 395 ($M+H^+$); 417 ($M+Na^+$).

2.

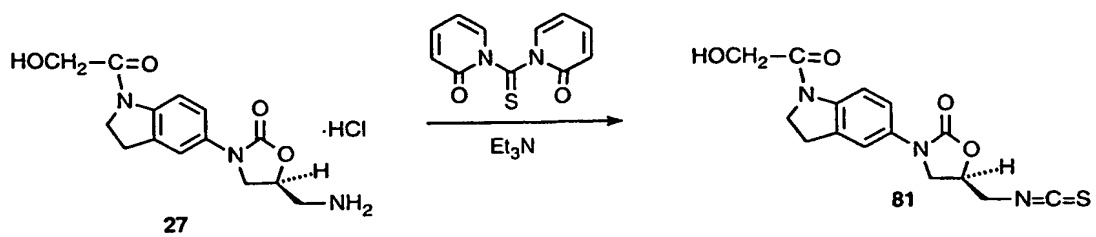


80 45

Excess anhydrous ammonia was bubbled into a stirred, ice cold solution of **80** (crude product from the previous reaction) in THF (25 mL) and the mixture was kept in the ice bath for 90 min and concentrated under a stream of nitrogen. The residue was chromatographed on silica gel with 5% MeOH-0.4% NH_4OH-$CHCl_3$ and the product was crystallized from acetonitrile to give 0.0544 g of **45**: mp 209-210 °C; ^1H NMR [300 MHz, $(CD_3)_2SO$] d 294 (broad s, 4H), 3.47 (broad s, 2H), 3.60 (broad s, 2H), 3.78 (broad s, 3H), 4.07 (t, 1H), 4.10 (d, J = 5.5 Hz, 2H), 4.63 (t, J = 5.5 Hz, 1H), 4.81 (broad s, 1H), 7.05 (t, 1H), 7.16 (d,d, 1H), 7.15 (broad s, 2H), 7.49 (d,d, 1H), 7.91 (t, 1H); IR (mull) 3443, 3403, 3321, 3202, 3081, 1753, 1655, 1648 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{23}FN_5O_4S$ ($M+H^+$) 412.1454, found 412.1447. Anal. calcd for $C_{17}H_{22}FN_5O_4S$: C, 49.63; H, 5.39; N, 17.02. Found: C, 49.63; H, 5.48; N, 16.99.

EXAMPLE 32: **(S)-N-[[3-[1-(Hydroxyacetyl)-5-indolinyl]-2-oxo-5-oxazolidinyl]methyl]thiourea (46).**

1.



27 81

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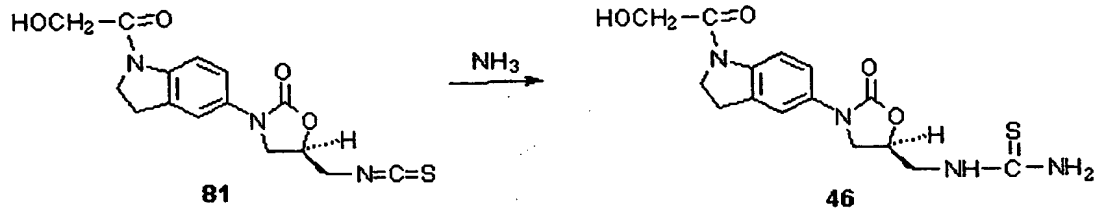
An ice cold, stirred solution of 1,1¢-thiocarbonyldi-2(1H)-pyridone (0.096 g, 0.41 mmol) in CH_2Cl_2 (5 mL) was treated with a suspension of **27** (0.10 g, 0.34 mmol) in CH_2Cl_2 (15 mL) and then with 0.05 mL (0.36 mmol) of triethylamine. It was kept in the ice bath for 30 min and at ambient temperature for 2 h, diluted with CH_2Cl_2, washed with water and brine, dried ($MgSO_4$) and concentrated. Chromatography ofthe residue on silica gel with 20-40% CH_3CN-CH_2Cl_2 gave 0.04 g of **81**.

2.

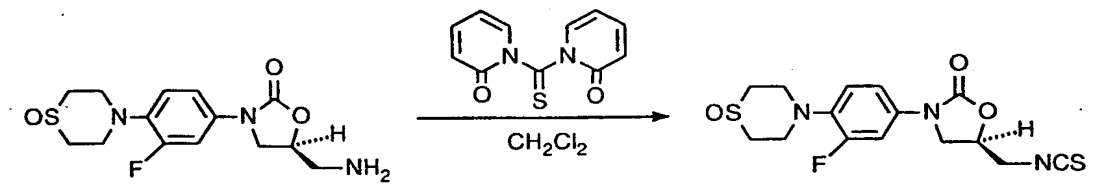


81 **46**

Excess anhydrous ammonia was bubbled into an ice cold solution of **81** (0.04 g) in THF (30 mL) and the mixture was kept in the ice bath for 80 min and concentrated under a stream of nitrogen. The residue was crystallized from CH_3CN to give 0.0151 g of **46**: mp 214-215 °C (dec); MS (FAB) *m/z* 351 ($M+H^+$), 350 (M^+), 319, 304, 147; HRMS (FAB) calcd for $C_{15}H_{19}N_4O_4S$ ($M+H^+$) 351.1127, found 351.1130; IR (DRIFT) 3329, 3296, 3196, 1746, 1655, 1626 cm^{-1}.

EXAMPLE 33: **(*S*)-N-[[3-[3-Fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea, thiomorpholine S-oxide (47).**

1.



33 **82**

A suspension of **33** (0.30 g, 0.92 mmol) in CH_2Cl_2 (7 mL) was added, during 20 min, to an ice cold, stirred mixture of 1,1¢-thiocarbonyldi-2(1H)-pyridone (0.258 g, 1.11 mmol) and CH_2Cl_2 (20 mL). The mixture was kept in the ice bath for 20 min and at ambient temperature for 2 h, mixed with CH_2Cl_2 (50 mL), washed with water and brine, dried ($MgSO_4$) and concentrated. Chromatography of the product on silica gel with 20-50% CH_3CN-CH_2Cl_2 gave 0.27 g of **82** which was used in the next reaction: MS(ES) *m/z* 370 ($M+H^+$), 392 ($M+Na^+$).

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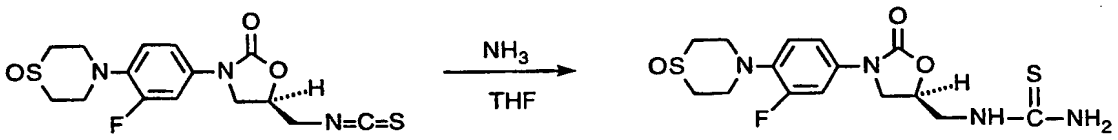
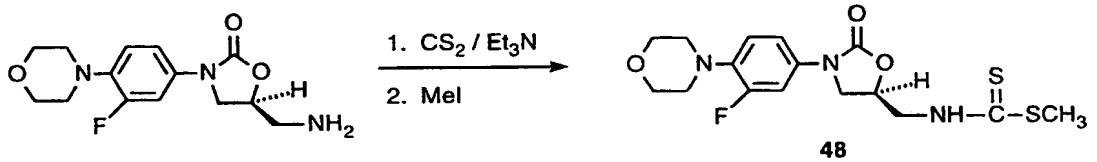
2.



82 47

A stirred, ice cold solution of **82** (0.27g , 0.73 mmol) in THF (15 mL), under nitrogen, was treated with excess anhydrous ammonia, kept in the ice bath for 1 h and concentrated; crystallization of the residue from MeOH gave 0.175 g of **47**; mp 212-213 °C; ^{1}H NMR [300 MHz, $(CD_3)_2SO$] d 2.83 (m, 2H), 3.01 (m, 2H), 3.17 (m, 2H), 3.50 (t, 2H), 3.78 (broad s, 3H), 4.08 (t, 1H), 4.80 (broad s, 1H), 7.17 (m, 2H), 7.17 (broad s, 2H), 7.50 (d, 1H), 7.90 (t, 1H); MS(ES) *m/z* 409 ($M+Na^+$); IR (mull) 3335, 3284, 3211, 3175, 3097, 1750, 1630 cm^{-1}. Anal. calcd for $C_{15}H_{19}FN_4O_3S_2$: C, 46.62; H, 4.95; N, 14.50. Found: C, 46.50; H, 4.95; N, 14.40.

EXAMPLE 34: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl-S-methyldithiocarbamate (48).**



39 48

An ice cold, stirred mixture of **39**[8] (0.59 g, 0.0020 mol), EtOH (1.5 mL), water (2 drops) and triethylamine (0.613 mL, 0.00440 mol), under nitrogen, was treated with carbon disulfide (0.066 mL, 0.0011 mol) and kept in the ice bath for 2 h and at ambient temperature for 18 h. (A solution was obtained after the addition of carbon disulfide; a white precipitate began to form soon after the mixture was warmed to ambient temperature.) The thick suspension was treated, dropwise during 2 min, with a solution of methyl iodide (0.137 mL, 0.00220 mol) in EtOH (2 mL) and the mixture was kept at ambient temperature for 1.5 h and concentrated in vacuo. A solution of the residue in EtOAc was washed with saturated $NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel with 1.8% MeOH-CH_2Cl_2 and the product was crystallized from EtOAc to give 0.197 g of **48**: mp 154-155 °C; IR (mull) 3354, 3346, 1726 cm^{-1}. Anal. calcd for $C_{16}H_{20}FN_3O_3S_2$: C, 49.85; H, 5.23; N, 10.90. Found: C, 49.73; H, 5.25; N, 10.82.

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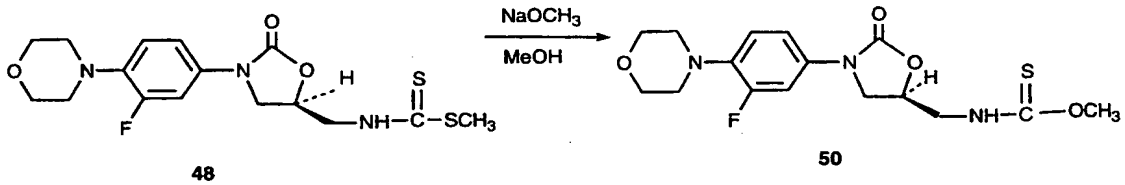
EXAMPLE 35: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl-O-methylthiocarbamate (50).**



48 50

A stirred mixture of **48** (0.200 g, 0.518 mmol), sodium methoxide (0.003 g, 0.06 mmol) and MeOH (5 mL), under nitrogen, was refluxed for 4 h and kept at ambient temperature for 18 h. It was found that the starting material and product had similar mobilities on TLC. the reaction was therefore followed by MS(ES). Starting material was still present. The mixture was refluxed for 3 h, additional sodium methoxide (0.005 g) was added and reflux was continued for 2 h. It was kept at ambient temperature for 18 h, refluxed for 1 h, kept at ambient temperature 1.5 h and concentrated in vacuo. The residue was mixed with ice, the pH was adjusted to 9-10 with 1M $KHSO_4$ and saturated $NaHCO_3$ and the mixture was extracted with CH_2Cl_2. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel with 5% acetone-CH_2Cl_2 and the product was crystallized from EtOAc-hexane to give 0.107 g of **50**: mp 128-129 °C; MS(ES) *m/z* 370 ($M+H^+$), 392 ($M+Na^+$); IR (DRIFT) 3282, 3251, 1753, 1735 cm^{-1}; ^1H NMR [300 MHz, $(CD_3)_2SO$] d 2.94 (m, 4H), 3.47, 374 (m,m, 7H), 3.86, 3.91 (s,s, 3H), 4.10 (m, 1H), 4.73, 4.86 (m,m, 1H), 7.05 (t, 1H), 7.16 (d,d, 1H), 7.47 (d,d, 1H), 9.41, 9.50 (s,s, 1H). Anal. calcd for $C_{16}H_{20}FN_3O_4S$: C, 52.02; H, 5.46; N, 11.38. Found: C, 51.97; H, 5.49; N, 11.35.

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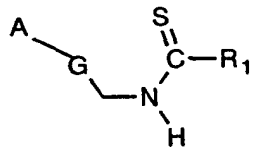
WHAT IS CLAIMED:

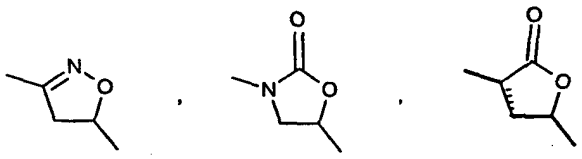
1. A compound of the formula I



I

or pharmaceutical acceptable salts thereof wherein:

G is



R_1 is

a) H,

b) NH_2,

c) NH-C_{1-4} alkyl,

d) C_{1-4} alkyl,

e) -OC_{1-4} alkyl,

f) -S C_{1-4} alkyl,

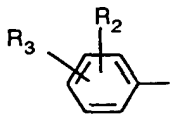
g) C_{1-4} alkyl substituted with 1-3 F, 1-2 Cl, CNor -COOC_{1-4} alkyl,

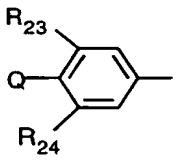
h) C_{3-6} cycloalkyl,

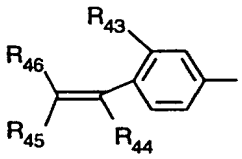
i) N(C_{1-4}) alkyl)$_2$ or

j) N(CH_2)$_{2-5}$;

A is

a) 

b)  ,

c)  ,

d) a 5-membered heteroaromatic moiety having one to three atoms selected from the group consisting of S, N, and O,

wherein the 5-membered heteroaromatic moiety is bonded via a carbon atom,

wherein the 5-membered heteroaromatic moiety can additionally have a fused-on benzene or naphthyl ring,

wherein the heteroaromatic moiety is optionally substituted with one to three R_{48},

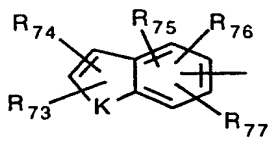
e) a 6-membered heteroaromatic moiety having at least one nitrogen atom,

wherein the heteroaromatic moiety is bonded via a carbon atom,

wherein the 6-membered heteroaromatic moiety can additionally have a fused-on benzene or naphthyl ring,

wherein the heteroaromatic moiety is optionally substituted with one to three R_{55},

f) a β-carbolin-3-yl, or indolizinyl bonded via the 6-membered ring, optionally substituted with one to three R_{55},

g)  , or

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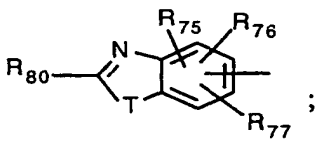
h) 

;

wherein R_2 is

a) H,
b) F,
c) Cl,
d) Br,
e) C_{1-3} alkyl,
f) NO_2, or
g) R_2 and R_3 taken together are $-O-(CH_2)_h-O-$;

R_3 is

a) $-S(=O)_i R_4$,
b) $-S(=O)_2-N=S(O)_jR_5R_6$,
c) $-SC(=O)R_7$,
d) $-C(=O)R_8$,
e) $-C(=O)R_9$,
f) $-C(=O)NR_{10}R_{11}$,
g) $-C(=NR_{12})R_8$,
h) $-C(R_8)(R_{11})-OR_{13}$,
i) $-C(R_9)(R_{11})-OR_{13}$,
j) $-C(R_8)(R_{11})-OC(=O)R_{13}$,
k) $-C(R_9)(R_{11})-OC(=O)R_{13}$,
l) $-NR_{10}R_{11}$,
m) $-N(R_{10})-C(=O)R_7$,
n) $-N(R_{10})-S(=O)_iR_7$,
o) $-C(OR_{14})(OR_{15})R_8$,
p) $-C(R_8)(R_{16})-NR_{10}R_{11}$, or
q) C_{1-8} alkyl substituted with one or more =O other than at alpha position, $-S(=O)_iR_{17}$, $-NR_{10}R_{11}$, C_{2-5} alkenyl, or C_{2-5} alkynyl;

R_4 is

a) C_{1-4} alkyl optionally substituted with one or more halos, OH, CN, $NR_{10}R_{11}$, or $-CO_2R_{13}$,

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b) C_{2-4} alkenyl,

c) $-NR_{16}R_{18}$,

d) $-N_3$,

e) $-NHC(=O)R_7$,

f) $-NR_{20}C(=O)R_7$,

g) $-N(R_{19})_2$,

h) $-NR_{16}R_{19}$, or

i) $-NR_{19}R_{20}$,

R_5 and R_6 at each occurrence are the same or different and are

a) C_{1-2} alkyl, or

b) R_5 and R_6 taken together are $-(CH_2)_k-$;

R_7 is C_{1-4} alkyl optionally substituted with one or more halos;

R_8 is

a) H, or

b) C_{1-8} alkyl optionally substituted with one or more halos, or C_{3-8} cycloalkyl;

R_9 is C_{1-4} alkyl substituted with one or more

a) $-S(=O)R_{17}$,

b) $-OR_{13}$,

c) $-OC(=O)R_{13}$,

d) $-NR_{10}R_{11}$, or

e) C_{1-5} alkenyl optionally substituted with CHO;

R_{10} and R_{11} at each occurrence are the same or different and are

a) H,

b) C_{1-4} alkyl, or

c) C_{3-8} cycloalkyl;

R_{12} is

a) $-NR_{10}R_{11}$,

b) $-OR_{10}$; or

c) $-NHC(=O)R_{10}$;

R_{13} is

a) H, or

b) C_{1-4} alkyl;

R_{14} and R_{15} at each occurrence are the same or different and are

a) C_{1-4} alkyl, or

b) R_{14} and R_{15} taken together are $-(CH)_l-$;

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R_{16} is

a) H,

b) C_{1-4} alkyl, or

c) C_{3-8} cycloalkyl;

R_{17} is

a) C_{1-4} alkyl, or

b) C_{3-8} cycloalkyl;

R_{18} is

a) H,

b) C_{1-4} alkyl,

c) C_{2-4} alkenyl,

d) C_{3-4} cycloalkyl,

e) $-OR_{13}$ or

f) $-NR_{21}R_{22}$;

R_{19} is

a) Cl,

b) Br, or

c) I;

R_{20} is a physiologically acceptable cation;

R_{21} and R_{22} at each occurrence are the same or different and are

a) H,

b) C_{1-4} alkyl, or

c) $-NR_{21}R_{22}$ taken together are $-(CH_2)_m-$;

wherein R_{23} and R_{24} at each occurrence are the same or different and are

a) H,

b) F,

c) Cl,

d) C_{1-2} alkyl,

e) CN

f) OH,

g) C_{1-2} alkoxy,

h) nitro, or

i) amino;

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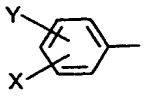
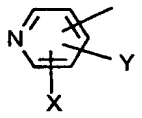
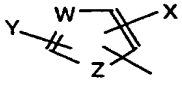
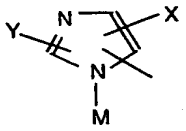
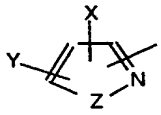
Q is

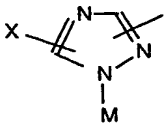
a)  ,

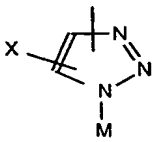
b)  ,

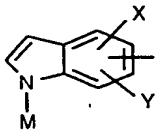
c)  ,

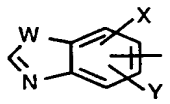
d)  ,

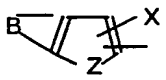
e)  ,

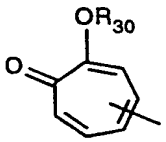
f)  ,

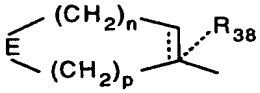
g)  ,

h)  ,

i)  ,

j) 

k)  ,

l)  ,

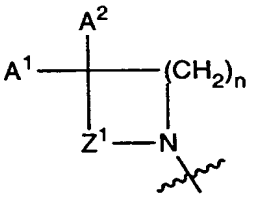
m) a diazinyl group optionally substituted with X and Y,

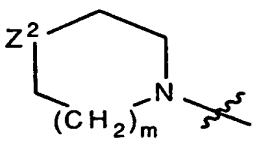
n) a triazinyl group optionally substituted with X and Y,

o) a quinolinyl group optionally substituted with X and Y,

p) a quinoxalinyl group optionally substituted with X and Y,

q) a naphthyridinyl group optionally substituted with X and Y,

r)  ,

s)  ,

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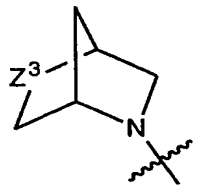
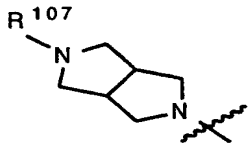
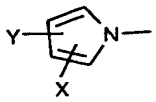
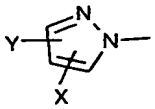
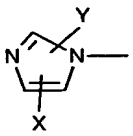
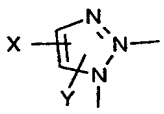
t)  ,

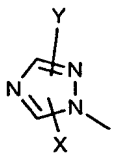
u)  ,

v)  ,

w)  ,

x)  ,

y)  ,

z)  ,

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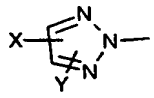
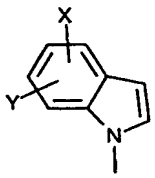
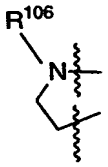
aa)  ,

bb)  or

Q and R_{24} taken together are

 ,

wherein Z^1 is

a) $-CH_2-$,

b) $-CH(R^{104})-CH_2-$,

c) -C(O)-, or

d) $-CH_2CH_2CH_2-$;

wherein Z^2 is

a) $-O_2S-$,

b) -O-,

c) $-N(R^{107})-$,

d) -OS-, or

e) -S-;

wherein Z^3 is

a) $-O_2S-$,

b) -O-,

c) -OS-, or

d) -S-;

wherein A^1 is

a) H-, or

b) CH_3;

wherein A^2 is

a) H-,

b) HO-,

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c) CH_3-,

d) CH_3O-,

e) $R^{102}O$-CH_2-C(O)-NH-

f) $R^{103}O$-C(O)-NH-,

g) $(C_1$-$C_2)$alkyl-O-C(O)-,

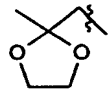
h) HO-CH_2-,

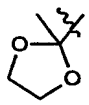
i) CH_3O-NH-,

j) $(C_1$-$C_3)$alkyl-O_2C-

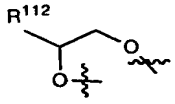
k) CH_3-C(O)-,

l) CH_3-C(O)-CH_2-,

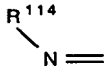
m)  , or

n)  ,

A^1 and A^2 taken together are:

a)  ,

b)  , or

c)  ;

wherein R^{102} is

a) H-,

b) CH_3-,

c) phenyl-CH_2-, or

d) $CH_3C(O)$-;

wherein R^{103} is

a) $(C_1$-$C_3)$alkyl-, or

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b) phenyl-;

wherein R^{104} is

a) H-, or

b) HO-;

wherein R^{105} is

a) H-,

b) $(C_1$-$C_3)$alkyl-,

c) $CH_2 = CH\text{-}CH_2$-, or

d) $CH_3\text{-}O\text{-}(CH_2)_2$-;

wherein R^{106} is

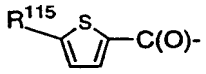
a) $CH_3\text{-}C(O)$-,

b) H-C(O)-,

c) $Cl_2CH\text{-}C(O)$-,

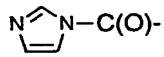
d) $HOCH_2\text{-}C(O)$-,

e) CH_3SO_2-,

f) 

,

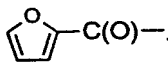
g) $F_2CHC(O)$-,

h) 

,

i) $H_3C\text{-}C(O)\text{-}O\text{-}CH_2\text{-}C(O)$-,

j) $H\text{-}C(O)\text{-}O\text{-}CH_2\text{-}C(O)$-,

k) 

,

l) $HC{\equiv}C\text{-}CH_2O\text{-}CH_2\text{-}C(O)$-, or

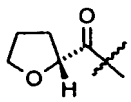
m) phenyl-CH_2-O-CH_2-C(O)-;

wherein R^{107} is

a) $R^{102}O\text{-}C(R^{110})(R^{111})\text{-}C(O)$-,

b) $R^{103}O\text{-}C(O)$-,

c) $R^{108}\text{-}C(O)$-,

d) 

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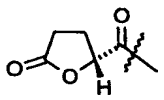
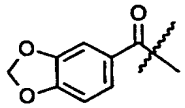
e)  ,

f) H_3C-C(O)-$(CH_2)_2$-C(O)-,

g) R^{109}-SO_2-,

h)  ,

i) HO-CH_2-C(O)-,

j) R^{116}-$(CH_2)_2$-,

k) R^{113}-C(O)-O-CH_2-C(O)-,

l) $(CH_3)_2N$-CH_2-C(O)-NH-,

m) NC-CH_2-, or

n) F_2-CH-CH_2-;

wherein R^{108} is

a) H-,

b) $(C_1$-$C_4)$alkyl,

c) aryl -$(CH_2)_p$,

d) ClH_2C-,

e) Cl_2HC-,

f) FH_2C-,

g) F_2HC-, or

h) $(C_3$-$C_6)$cycloalkyl;

wherein R^{109} is

a) -CH_3,

b) -CH_2Cl

c) -CH_2CH=CH_2,

d) aryl, or

e) -CH_2CN;

wherein R^{110} and R^{111} are independently

a) H-,

b) CH_3-; or

wherein R^{112} is

a) H-,

b) CH_3O-CH_2O-CH_2-, or

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c) $HOCH_2$-;

wherein R^{113} is

a) CH_3-,

b) $HOCH_2$-,

c) $(CH_3)_2N$-phenyl, or

d) $(CH_3)_2N$-CH_2-;

wherein R^{114} is

a) HO-,

b) CH_3O-,

c) H_2N-,

d) CH_3O-C(O)-O-,

e) CH_3-C(O)-O-CH_2-C(O)-O-,

f) phenyl-CH_2-O-CH_2-C(O)-O-,

g) HO-$(CH_2)_2$-O-,

h) CH_3O-CH_2-O-$(CH_2)_2$-O-, or

i) CH_3O-CH_2-O-;wherein R^{113} is

a) CH_3-,

b) $HOCH_2$-,

c) $(CH_3)_2N$-phenyl, or

d) $(CH_3)_2N$-CH_2-;

wherein R^{115} is

a) H-, or

b) Cl-;

wherein R^{116} is

a) HO-

b) CH_3O-, or

c) F;

B is an unsaturated 4-atom linker having one nitrogen and three carbons;

M is

a) H,

b) C_{1-8} alkyl,

c) C_{3-8} cycloalkyl,

d) -$(CH_2)_m$$OR_{13}$, or

e) -$(CH_2)_h$-$NR_{21}R_{22}$;

Z is

a) O,

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b) S, or

c) NM;

W is

a) CH,

b) N, or

c) S or O when Z is NM;

Y is

a) H,

b) F,

c) Cl,

d) Br,

e) C_{1-3} alkyl, or

f) NO_2;

X is

a) H,

b) -CN,

c) OR_{27},

d) halo,

e) NO_2,

f) tetrazoyl,

g) -SH,

h) $-S(=O)_iR_4$,

i) $-S(=O)_2-N=S(O)_jR_5R_6$,

j) $-SC(=O)R_7$,

k) $-C(=O)R_{25}$,

l) $-C(=O)NR_{27}R_{28}$,

m) $-C(=NR_{29})R_{25}$,

n) $-C(R_{25})(R_{28})-OR_{13}$,

o) $-C(R_{25})(R_{28})-OC(=O)R_{13}$,

p) $-C(R_{28})(OR_{13})-(CH_2)_h-NR_{27}R_{28}$,

q) $-NR_{27}R_{28}$,

r) $-N(R_{27})C(=O)R_7$,

s) $-N(R_{27})-S(=O)_iR_7$,

t) $-C(OR_{14})(OR_{15})R_{28}$,

u) $-C(R_{25})(R_{16})-NR_{27}R_{26}$, or

v) C_{1-8} alkyl substituted with one or more halos, OH, =O other than at

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alpha position, $-S(=O)_iR_{17}$, $-NR_{27}R_{28}$, C_{2-5} alkenyl, C_{2-5} alkynyl, or C_{3-8} cycloalkyl;

R_4, R_5, R_6, R_7, R_{13}, R_{14}, R_{15}, R_{16}, and R_{17} are the same as defined above;

R_{25} is

a) H,

b) C_{1-8} alkyl optionally substituted with one or more halos, C_{3-8} cycloalkyl, C_{1-4} alkyl substituted with one or more of $-S(=O)_iR_{17}$, $-OR_{13}$, or $OC(=O)R_{13}$, $NR_{27}R_{28}$, or

c) C_{2-5} alkenyl optionally substituted with CHO, or CO_2R_{13};

R_{26} is

a) R_{28}, or

b) $NR_{27}N_{28}$;

R_{27} and R_{28} at each occurrence are the same or different and are

a) H,

b) C_{1-8} alkyl,

c) C_{3-8} cycloalkyl,

d) $-(CH_2)_mOR_{13}$,

e) $-(CH_2)_h-NR_{21}R_{22}$, or

f) R_{27} and R_{28} taken together are $-(CH_2)_2O(CH_2)_2-$, $-(CH_2)_hCH(COR_7)-$, or $-(CH_2)_2N(CH_2)_2(R_7)$;

R_{29} is

a) $-NR_{27}R_{28}$,

b) $-OR_{27}$, or

c) $-NHC(=O)R_{28}$;

wherein R_{30} is

a) H,

b) C_{1-8} alkyl optionally substituted with one or more halos, or

c) C_{1-8} alkyl optionally substituted with one or more OH, or C_{1-6} alkoxy;

wherein E is

a) NR_{39},

b) $-S(=O)_i$, or

c) O;

R_{38} is

a) H,

b) C_{1-6} alkyl,

c) $-(CH_2)_q$-aryl, or

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d) halo;

R_{39} is

a) H,

b) C_{1-6} alkyl optionally substituted with one or more OH, halo, or -CN,

c) $-(CH_2)_q$-aryl,

d) $-CO_2R_{40}$,

e) $-COR_{41}$,

f) $-C(=O)-(CH_2)_q-C(=O)R_{40}$,

g) $-S(=O)_2-C_{1-6}$ alkyl,

h) $-S(=O)_2-(CH_2)_q$-aryl, or

i) $-(C=O)_j$-Het;

R_{40} is

a) H,

b) C_{1-6} alkyl optionally substituted with one or more OH, halo, or -CN,

c) $-(CH_2)_q$-aryl, or

d) $-(CH_2)_q-OR_{42}$;

R_{41} is

a) C_{1-6} alkyl optionally substituted with one or more OH, halo, or -CN,

b) $-(CH_2)_q$-aryl, or

c) $-(CH_2)_q-OR_{42}$;

R_{42} is

a) H,

b) C_{1-6} alkyl,

c) $-(CH_2)_q$-aryl, or

d) $-C(=O)-C_{1-6}$ alkyl;

aryl is

a) phenyl,

b) pyridyl, or

c) napthyl; a to c optionally substituted with one or more halo, -CN, OH, SH, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} alkylthio;

wherein R_{43} is

a) H,

b) C_{1-2} alkyl,

c) F, or

d) OH;

R_{44} is

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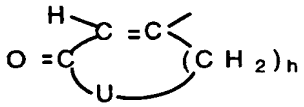
a) H,

b) CF_3,

c) C_{1-3} alkyl optionally substituted with one or more halo,

d) phenyl optionally substituted with one or more halo,

e) R_{44} and R_{45} taken together are a 5-, 6-, or 7-membered ring of the formula,

or 

f) R_{44} and R_{45} taken together are $-(CH_2)_k-$, when R_{46} is an electron-withdrawing group;

R_{45} and R_{46} at each occurrence are the same or different and are

a) an electron-withdrawing group,

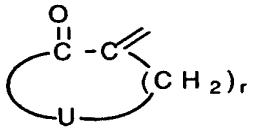
b) H,

c) CF_3,

d) C_{1-3} alkyl optionally substituted with one halo,

e) phenyl, provided at least one of R_{45} or R_{46} is an electron-withdrawing group, or

f) R_{45} and R_{46} taken together are a 5-, 6-, 7-membered ring of the formula



;

U is

a) CH_2,

b) O,

c) S, or

d) NR_{47};

R_{47} is

a) H, or

b) C_{1-5} alkyl;

wherein R_{48} is

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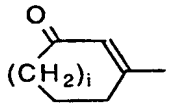
a) carboxyl,
b) halo,
c) -CN,
d) mercapto,
e) formyl,
f) CF_3,
g) $-NO_2$,
h) C_{1-6} alkoxy,
i) C_{1-6} alkoxycarbonyl,
j) C_{1-6} alkythio,
k) C_{1-6} acyl,
l) $-NR_{49}R_{50}$,
m) C_{1-6} alkyl optionally substituted with OH, C_{1-5} alkoxy, C_{1-5} acyl, or $-NR_{49}R_{50}$,
n) C_{2-8} alkenylphenyl optionally substituted with one or two R_{51},
o) phenyl optionally substituted with one or two R_{51},
p) a 5-, or 6-membered (un)saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with one or two R_{51}, or
q)  ;

R_{49} and R_{50} at each occurrence are the same or different and are
a) H,
b) C_{1-4} alkyl,
c) C_{5-6} cycloalkyl, or
d) R_{49} and R_{50} taken together with the nitrogen atom is a 5-, 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, and O, and can in turn be optionally substituted with, including on the further nitrogen atom, C_{1-3} alkyl, or C_{1-3} acyl;

R_{51} is
a) carboxyl,
b) halo,
c) -CN,
d) mercapto,

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e) formyl,
f) CF_3,
g) $-NO_2$,
h) C_{1-6} alkoxy,
i) C_{1-6} alkoxycarbonyl,
j) C_{1-6} alkythio,
k) C_{1-6} acyl,
l) C_{1-6} alkyl optionally substituted with OH, C_{1-5} alkoxy, C_{1-5} acyl, or $-NR_{49}R_{50}$,
m) phenyl,
n) $-C(=O)NR_{52}\ R_{53}$,
o) $-NR_{49}R_{50}$,
p) $-N(R_{52})(-SO_2R_{54})$,
q) $-SO_2-NR_{52}R_{53}$, or
r) $-S(=O)_iR_{54}$;

R_{52} and R_{53} at each occurrence are the same or different and are
a) H,
b) C_{1-6} alkyl, or
c) phenyl;

R_{54} is
a) C_{1-4} alkyl, or
b) phenyl optionally substituted with C_{1-4} alkyl;

wherein R_{55} is
a) carboxyl,
b) halo,
c) -CN,
d) mercapto,
e) formyl,
f) CF_3,
g) $-NO_2$,
h) C_{1-6} alkoxy,
i) C_{1-6} alkoxycarbonyl,
j) C_{1-6} alkythio
k) C_{1-6} acyl,
l) $-NR_{56}\ R_{57}$,
m) C_{1-6} alkyl optionally substituted with OH, C_{1-5} alkoxy, C_{1-5} acyl, or

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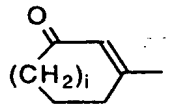
$-NR_{56}R_{57}$,

n) C_{2-8} alkenylphenyl optionally substituted with one or two R_{58},

o) phenyl optionally substituted with one or two R_{58},

p) a 5- or 6-membered (un)saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with one or two R_{58}, or

q)  ;

R_{56} and R_{57} at each occurrence are the same or different and are

a) H,

b) formyl,

c) C_{1-4} alkyl,

d) C_{1-4} acyl,

e) phenyl,

f) C_{3-6} cycloalkyl, or

g) R_{56} and R_{57} taken together with the nitrogen atom is a 5-, 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, and O, and can in turn be optionally substituted with, including on the further nitrogen atom, phenyl, pyrimidyl, C_{1-3} alkyl, or C_{1-3} acyl;

R_{58} is

a) carboxyl,

b) halo,

c) -CN,

d) mercapto,

e) formyl,

f) CF_3,

g) $-NO_2$,

h) C_{1-6} alkoxy,

i) C_{1-6} alkoxycarbonyl,

j) C_{1-6} alkythio,

k) C_{1-6} acyl,

l) phenyl,

m) C_{1-6} alkyl optionally substituted with OH, azido, C_{1-5} alkoxy, C_{1-5} acyl,

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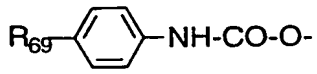
$-NR_{65}R_{66}$, $-SR_{67}$, $-O-SO_2R_{68}$, or



n) $-C(=O)NR_{59}\ R_{60}$,

o) $-NR_{56}R_{57}$,

p) $-N(R_{59})(-SO_2R_{54})$,

q) $-SO_2-NR_{59}R_{60}$,

r) $-S(=O)_iR_{54}$,

s) $-CH=N-R_{61}$, or

t) $-CH(OH)-SO_3R_{64}$;

R_{54} is the same as defined above;

R_{59} and R_{60} at each occurrence are the same or different and are

a) H,

b) C_{1-6} alkyl,

c) phenyl, or

d) tolyl;

R_{61} is

a) OH,

b) benzyloxy,

c) $-NH-C(=O)-NH_2$,

d) $-NH-C(=S)-NH_2$, or

e) $-NH-C(=NH)-NR_{62}R_{63}$;

R_{62} and R_{63} at each occurrence are the same or different and are

a) H, or

b) C_{1-4} alkyl optionally substituted with phenyl or pyridyl;

R_{64} is

a) H, or

b) a sodium ion;

R_{65} and R_{66} at each occurrence are the same or different and are

a) H,

b) formyl,

c) C_{1-4} alkyl,

d) C_{1-4} acyl,

e) phenyl,

f) C_{3-6} cycloalkyl,

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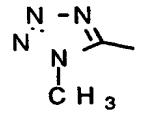
g) R_{65} and R_{66} taken together are a 5-, 6-membered saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with, including on the nitrogen atom, phenyl, pyrimidyl, C_{1-3} alkyl, or C_{1-3} acyl,

h) $-P(O)(OR_{70})(OR_{71})$, or

i) $-SO_2-R_{72}$;

R_{67} is



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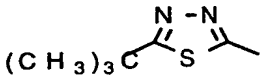

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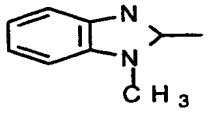

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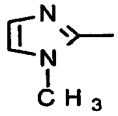

;

R_{68} is C_{1-3} alkyl;

R_{69} is

a) C_{1-6} alkoxycarbonyl, or

b) carboxyl;

R_{70} and R_{71} at each occurrence are the same or different and are

a) H, or

b) C_{1-3} alkyl;

R_{72} is

a) methyl,

b) phenyl, or

c) tolyl;

wherein K is

a) O, or

b) S;

R_{73}, R_{74}, R_{75}, R_{76}, and R_{77} at each occurrence are the same or different and are

a) H,

b) carboxyl,

c) halo,

d) -CN,

e) mercapto,

f) formyl,

g) CF_3,

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h) $-NO_2$,

i) C_{1-6} alkoxy,

j) C_{1-6} alkoxycarbonyl,

k) C_{1-6} alkythio,

l) C_{1-6} acyl,

m) $-NR_{78}R_{79}$,

n) C_{1-6} alkyl optionally substituted with OH, C_{1-5} alkoxy, C_{1-5} acyl, $-NR_{78}R_{79}$, -N(phenyl)(CH_2-CH_2-OH), -O-CH(CH_3)(OCH_2CH_3), or -O-phenyl-[para-NHC(=O)CH_3],

o) C_{2-8} alkenylphenyl optionally substituted with R_{51},

p) phenyl optionally substituted with R_{51}, or

q) a 5-, or 6-membered (un)saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with R_{51};

R_{51} is the same as defined above;

R_{78} and R_{79} at each occurrence are the same or different and are

a) H,

b) C_{1-4} alkyl,

c) phenyl, or

d) R_{78} and R_{79} taken together with the nitrogen atom is a 5-, 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, and O, and can in turn be optionally substituted with, including on the further nitrogen atom, C_{1-3} alkyl, or C_{1-3} acyl;

wherein T is

a) O,

b) S, or

c) SO_2;

R_{75}, R_{76}, and R_{77} are the same as defined above;

R_{80} is

a) H,

b) formyl,

c) carboxyl,

d) C_{1-6} alkoxycarbonyl,

e) C_{1-8} alkyl,

f) C_{2-8} alkenyl,

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wherein the substituents (e) and (f) can be optionally substituted with OH, halo, C_{1-6} alkoxy, C_{1-6} acyl, C_{1-6} alkylthio or C_{1-6} alkoxycarbonyl, or phenyl optionally substituted with halo,

g) an aromatic moiety having 6 to 10 carbon atoms optionally substituted with carboxyl, halo, -CN, formyl, CF_3, $-NO_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} acyl, C_{1-6} alkylthio, or C_{1-6} alkoxycarbonyl;

h) $-NR_{81}R_{82}$,

i) $-OR_{90}$,

j) $-S(=O)_i-R_{91}$,

k) $-SO_2-N(R_{92})(R_{93})$, or

l) a radical of the following formulas:

R_{81} and R_{82} at each occurrence are the same or different and are

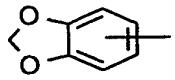
a) H,

b) C_{3-6} cycloalkyl,

c) phenyl,

d) C_{1-6} acyl,

e) C_{1-8} alkyl optionally substituted with OH, C_{1-6} alkoxy which can be substituted with OH, a 5-, or 6-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, phenyl optionally substituted with OH, CF_3, halo, $-NO_2$, C_{1-4} alkoxy, $-NR_{83}R_{84}$, or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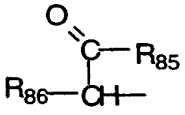
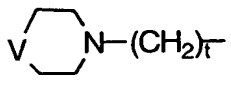
f) 
, or

g) 
;

V is

a) O,

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b) CH_2, or

c) NR_{87};

R_{83} and R_{84} at each occurrence are the same or different and are

a) H, or

b) C_{1-4} alkyl;

R_{85} is

a) OH,

b) C_{1-4} alkoxy, or

c) $-NR_{88}R_{89}$;

R_{86} is

a) H, or

b) C_{1-7} alkyl optionally substituted with indolyl, OH, mercaptyl, imidazoly, methylthio, amino, phenyl optionally substituted with OH, $-C(=O)-NH_2$, $-CO_2H$, or $-C(=NH)-NH_2$;

R_{87} is

a) H,

b) phenyl, or

c) C_{1-6} alkyl optionally substituted by OH;

R_{88} and R_{89} at each occurrence are the same or different and are

a) H,

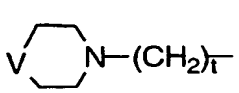
b) C_{1-5} alkyl

c) C_{3-6} cycloalky, or

d) phenyl;

R_{90} is

a) C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy or C_{1-6} hydroxy, C_{3-6} cycloalkyl, a 6-membered aromatic optionally benzo-fused heterocyclic moiety having one to three nitrogen atoms, which can in turn be substituted with one or two $-NO_2$, CF_3, halo, -CN, OH, C_{1-5} alkyl, C_{1-5} alkoxy, or C_{1-5} acyl;

b)  ,

c) phenyl, or

d) pyridyl;

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R_{91} is

a) C_{1-16} alkyl,

b) C_{2-16} alkenyl,

wherein the substituents (a) and (b) can be optionally substituted with C_{1-6} alkoxycarbonyl, or a 5-, 6-, 7-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,

c) an aromatic moiety having 6 to 10 carbon atoms, or

d) a 5-, 6-, 7-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,

wherein the substituents (c) and (d) can be optionally substituted with carboxyl, halo, -CN, formyl, CF_3, $-NO_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} acyl, C_{1-6} alkylthio, or C_{1-6} alkoxycarbonyl;

R_{92} and R_{93} at each occurrence are the same or different and are

a) H,

b) phenyl,

c) C_{1-6} alkyl, or

d) benzyl;

R_{94} and R_{95} at each occurrence are the same or different and are

a) H,

b) OH,

c) C_{1-6} alkyl optionally substituted with $-NR_{83}R_{84}$, or

d) R_{94} and R_{95} taken together are =O;

R_{96} is

a) an aromatic moiety having 6 to 10 carbon atoms,

b) a 5-, or 6-membered aromatic optionally benzo-fused heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,

wherein the substituents (a) and (b) which can in turn be substituted with one or three $-NO_2$, CF_3, halo, -CN, OH, phenyl, C_{1-5} alkyl, C_{1-5} alkoxy, or C_{1-5} acyl,

c) morpholinyl,

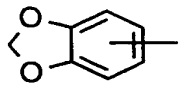
d) OH,

e) C_{1-6} alkoxy,

f) $-NR_{83}R_{84}$,

g) $-C(=O)-R_{97}$, or

ENSDOCID: <WO 9854161A1 | >

h)  ;

R_{97} is

a) morpholinyl,

b) OH, or

c) C_{1-6} alkoxy;

h is 1, 2, or 3;

i is 0, 1, or 2;

j is 0 or 1;

k is 3, 4, or 5;

l is 2 or 3;

m is 4 or 5;

n is 0, 1, 2, 3, 4, or 5;

p is 0, 1, 2, 3, 4, or 5; with the proviso that n and p together are 1, 2, 3, 4, or 5;

q is 1, 2, 3, or 4;

r is 2, 3, or 4;

t is 0, 1, 2, 3, 4, 5, or 6;

u is 1 or 2.

2. A compound of Claim 1 which is :

a) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;

b) (S)-N-[[3-[3-Fluoro-4-[4-(5-methyl-1,3,4-thiadiazol-2-yl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;

c) (S)-N-[[3-[3-Fluoro-4-[2′,5′-dioxospiro[piperidine-4,4′-imidazolidine]-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;

d) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;

e) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea;

f) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-N′-methylthiourea;

g) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-thioformamide;

h) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-

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oxazolidinyl]methyl]thiopropion-amide;

i) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-2-chlorothioacetamide;

j) (S)-N-[[3-[3-Fluoro-4-(4-moropholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α,α,α-trifluorothioacetamide;

k) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α-fluorothioacetamide;

l) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α,α-difluorothioacetamide;

m) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α-cyanothioacetamide;

n) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α,α-dichlorothioacetamide;

o) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α-(methoxycarbonyl)thioacetamide;

p) (S)-N-[[3-[4-[1-[1,2,4]Triazolyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;

q) (S)-N-[[3-[4-[1-[1,2,4]Triazolyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;

r)) (S)-N-[[3-[1-(Hydroxyacetyl)-5-indolinyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;

s) (S)-N-[[3-[3-Fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;

t) (S)-N-[[3-[3-Fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thio-acetamide;

u) (S)-N-[[3-[3-Fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thio-acetamide, thiomorpholine S-oxide;

v) (S)-N-[[3-[3-Fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thio-acetamide, thiomorpholine S, S-dioxide;

w) (S)-N-[[3-[3,5-Difluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;

x) (S)-N-[[3-[4-[1-[1,2,4]Triazolyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea;

y) (*S*)-N-[[3-[3-Fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]-methyl]thiourea;

z) (S)-N-[[3-[1-(Hydroxyacetyl)-5-indolinyl]-2-oxo-5-

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oxazolidinyl]methyl]thiourea;

aa) (S)-N-[[3-[3-Fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methylthiourea, thiomorpholine S-oxide;

bb) (*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl-S-methyldithiocarbamate;

3. A method for treating microbial infections in patients comprising administering to a patient in need thereof an effective amount of a compound of Formula I.

BNSDOCID: <WO 9854161A1 | >

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/09889

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D263/20 C07D417/12 C07D413/10 C07D413/04 A61K31/42 C07D261/04 C07D307/32 C07D471/10 //(C07D471/10,235:00, 221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 127 902 A (E.I.DU PONT DE NEMOURS AND COMPANY) 12 December 1984 see claims ---	1-3
Y	EP 0 184 170 A (E.I. DU PONT DE NEMOURS AND COMPANY) 11 June 1986 see claims ---	1-3
Y	EP 0 359 418 A (THE UPJOHN COMPANY) 21 March 1990 see claims ---	1-3
Y	WO 95 07271 A (THE UPJOHN COMPANY) 16 March 1995 see claims ---	1-3
Y	WO 97 14690 A (ZENECA LTD) 24 April 1997 see claims ---	1-3

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 August 1998	21/08/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Henry, J

3

Form PCT/ISA/210 (second sheet) (July 1992)

BNSDOCID: <WO 9854161A1 I >

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/09889

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,Y	EP 0 789 025 A (BAYER AG) 13 August 1997 see page 33 - page 41; claims	1-3
P,Y	WO 98 07708 A (PHARMACIA & UPJOHN COMPANY) 26 February 1998 see claims	1-3
P,Y	DE 196 01 264 A (BAYER AG) 17 July 1997 see page 20 - page 23; claims	1-3

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

BNSDOCID: <WO 9854161A1 I >

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/09889

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 3
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 3 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: not applicable
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

B x II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark n Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

RNSDOCID: <WO 9854161A1 I >

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: not applicable

In view of the extremely broad Markush claims, the search was executed with due regard to the PCT Search Guidelines (PCT/GL/2), C-III, paragraph 2.1, 2.3 read in conjunction with 3.7 and Rule 33.3 PCT, i.e. particular emphasis was put on the inventive concept, as illustrated by the examples and the compounds of claim 2.
The international search was, in so far as possible and reasonable, complete in that it covered the entire subject-matter to which the claims are directed.

BNSDOCID: <WO 9854161A1 | >

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/09889

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0127902 A	12-12-1984	AU 583250 B	27-04-1989
		AU 2909984 A	13-12-1984
		CA 1254213 A	16-05-1989
		CA 1275652 A	30-10-1990
		DE 3485162 A	21-11-1991
		DK 279584 A	08-12-1984
		FI 842273 A,B	08-12-1984
		JP 60008277 A	17-01-1985
		MX 169619 B	15-07-1993
		SU 1505442 A	30-08-1989
		SU 1426451 A	23-09-1988
		US 4705799 A	10-11-1987
EP 0184170 A	11-06-1986	AU 611627 B	20-06-1991
		AU 5081685 A	11-06-1987
		CA 1260948 A	26-09-1989
		DE 3584427 A	21-11-1991
		DK 561885 A	06-06-1986
		FI 854804 A,B	06-06-1986
		IE 58325 B	08-09-1993
		JP 61134379 A	21-06-1986
		PT 81610 B	21-04-1988
		SU 1528317 A	07-12-1989
		US 4705799 A	10-11-1987
EP 0359418 A	21-03-1990	AT 112773 T	15-10-1994
		AU 617871 B	05-12-1991
		AU 4195789 A	02-04-1990
		CA 1335103 A	04-04-1995
		DE 68918792 D	17-11-1994
		DK 45591 A	13-03-1991
		EP 0434714 A	03-07-1991
		EP 0609905 A	10-08-1994
		JP 4500665 T	06-02-1992
		WO 9002744 A	22-03-1990
		US 5164510 A	17-11-1992
		US 5182403 A	26-01-1993
		US 5225565 A	06-07-1993
WO 9507271 A	16-03-1995	AU 687866 B	05-03-1998

BNSDOCID: <WO 9854161A1 I >

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/09889

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9507271 A		AU 7557094 A	27-03-1995
		CA 2168560 A	16-03-1995
		CN 1130379 A	04-09-1996
		EP 0717738 A	26-06-1996
		JP 9502436 T	11-03-1997
		ZA 9405894 A	05-02-1996
WO 9714690 A	24-04-1997	AU 7224896 A	07-05-1997
EP 0789025 A	13-08-1997	DE 19604223 A	07-08-1997
		AU 1251697 A	14-08-1997
		CA 2196862 A	07-08-1997
		CN 1160051 A	24-09-1997
		CZ 9700340 A	13-08-1997
		HR 970048 A	30-04-1998
		JP 9316073 A	09-12-1997
		NO 970511 A	07-08-1997
		PL 318277 A	18-08-1997
		SK 15897 A	08-10-1997
WO 9807708 A	26-02-1998	AU 3973697 A	06-03-1998
DE 19601264 A	17-07-1997	AU 1009897 A	24-07-1997
		CA 2194938 A	17-07-1997
		CZ 9700129 A	13-08-1997
		EP 0785200 A	23-07-1997
		HR 960615 A	28-02-1998
		JP 9194482 A	29-07-1997
		NO 970175 A	17-07-1997
		PL 317929 A	21-07-1997
		SK 5997 A	10-09-1997

BNSDOCID: <WO 9854161A1 I >

CORRECTED VERSION*

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 263/20, 417/12, 413/10, 413/04, A61K 31/42, C07D 261/04, 307/32, 471/10 // (C07D 471/10, 235:00, 221:00)

A1

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(43) International Publication Date: 3 December 1998 (03.12.98)

(21) International Application Number: PCT/US98/09889

(22) International Filing Date: 18 May 1998 (18.05.98)

(30) Priority Data:
60/048,342 30 May 1997 (30.05.97) US

(71) Applicant *(for all designated States except US)*: PHARMACIA & UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).

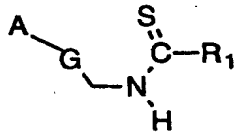
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: HESTER, Jackson, B., Jr. [US/US]; 9219 East ML Avenue, Galesburg, MI 49053 (US). NIDY, Eldon, George [US/US]; 3103 Morgan Street, Kalamazoo, MI 49001 (US). PERRICONE, Salvatore, Charles [US/US]; 7011 Division Avenue, Delton, MI 49046 (US). POEL, Toni-Jo [US/US]; 304 Anderson, Wayland, MI 49348 (US).

(74) Agent: YANG, Lucy, X.; Pharmacia & Upjohn Company, Intellectual Property Legal Services, 301 Henrietta Street, Kalamazoo, MI 49001 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: OXAZOLIDINONE ANTIBACTERIAL AGENTS HAVING A THIOCARBONYL FUNCTIONALITY



(I)

(57) Abstract

The present invention provides compounds of Formula (I) or pharmaceutical acceptable salts thereof wherein A, G and R_1 are as defined in the claims which are antibacterial agents.

*(Referred to in PCT Gazette No. 14/1999, Section II)

BNSDOCID: <WO 9854161A1 IA>

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CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

BNSDOCID: <WO 9854161A1 IA>

OXAZOLIDINONE ANTIBACTERIAL AGENTS HAVING A THIOCARBONYL FUNCTIONALITY

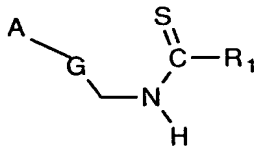
BACKGROUND OF THE INVENTION

The present invention relates to new and useful oxazolidinone compounds and their preparations, and more particularly to oxazolidinone compounds in which the carbonyl functionality of -NH-C(O)-R is converted to a thiocarbonyl functionality, such as a thiourea -NH-C(S)-NH_2, an alkyl thiourea -NH-C(S)-NH-(C_{1-4} alkyl), thioamide -NH-C(S)-(C_{1-4} alkyl) or -NH-C(S)-H.

Replacement of the oxygen atom with a sulfur atom has unexpectedly improved the antimicrobial properties of the compounds. The compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens, including Gram-positive aerobic bacteria such as multiply-resistant staphylococci and streptococci, Gram-negative organisms such as H. *influenzae* and M. *catarrahlis* as well as anaerobic organisms such as bacteroides and clostridia species, and acid-fast organisms such as *Mycobacterium tuberculosis* and *Mycobacterium avium*. The compounds are particularly useful because they are effective against the latter organisms which are known to be responsible for infection in persons with AIDS.

SUMMARY OF THE INVENTION

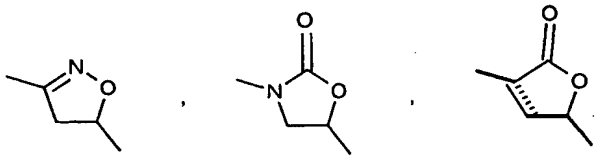
In one aspect the subject invention is a compound of the Formula I



I

or pharmaceutical acceptable salts thereof wherein:

G is



RNSDOCID: <WO 9854161A1 IA>

R_1 is

a) H,

b) NH_2,

c) NH-C_{1-4} alkyl,

d) C_{1-4} alkyl,

e) -OC_{1-4} alkyl,

f) -S C_{1-4} alkyl,

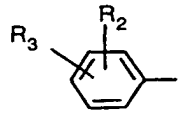
g) C_{1-4} alkyl substituted with 1-3 F, 1-2 Cl, CN or -COOC_{1-4} alkyl,

h) C_{3-6} cycloalkyl,

i) N(C_{1-4} alkyl)$_2$ or

j) N(CH_2)$_{2-5}$;

A is

a) 

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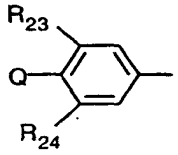
b) 

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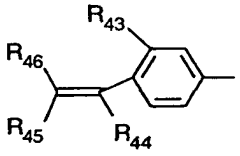
c) 

,

d) a 5-membered heteroaromatic moiety having one to three atoms selected from the group consisting of S, N, and O,

wherein the 5-membered heteroaromatic moiety is bonded via a carbon atom,

wherein the 5-membered heteroaromatic moiety can additionally have a fused-on benzene or naphthyl ring,

wherein the heteroaromatic moiety is optionally substituted with one to three R_{48},

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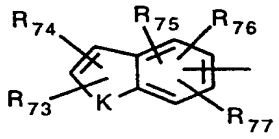
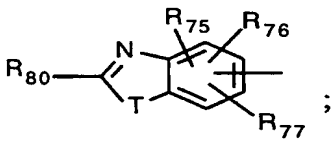
e) a 6-membered heteroaromatic moiety having at least one nitrogen atom,
wherein the heteroaromatic moiety is bonded via a carbon atom,
wherein the 6-membered heteroaromatic moiety can additionally have a fused-on benzene or naphthyl ring,
wherein the heteroaromatic moiety is optionally substituted with one to three R_{55},

f) a β-carbolin-3-yl, or indolizinyl bonded via the 6-membered ring, optionally substituted with one to three R_{55},

g)  , or

h)  ;

wherein R_2 is

a) H,
b) F,
c) Cl,
d) Br,
e) C_{1-3} alkyl,
f) NO_2, or
g) R_2 and R_3 taken together are -O-$(CH_2)_h$-O-;

R_3 is

a) -S(=O)$_i$ R_4,
b) -S(=O)$_2$-N=S(O)$_j$$R_5$$R_6$,
c) -SC(=O)R_7,
d) -C(=O)R_8,
e) -C(=O)R_9,
f) -C(=O)N$R_{10}$$R_{11}$,

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g) $-C(=NR_{12})R_8$,

h) $-C(R_8)(R_{11})-OR_{13}$,

i) $-C(R_9)(R_{11})-OR_{13}$,

j) $-C(R_8)(R_{11})-OC(=O)R_{13}$,

k) $-C(R_9)(R_{11})-OC(=O)R_{13}$,

l) $-NR_{10}R_{11}$,

m) $-N(R_{10})-C(=O)R_7$,

n) $-N(R_{10})-S(=O)_iR_7$,

o) $-C(OR_{14})(OR_{15})R_8$,

p) $-C(R_8)(R_{16})-NR_{10}R_{11}$, or

q) C_{1-8} alkyl substituted with one or more =O other than at alpha position, $-S(=O)_iR_{17}$, $-NR_{10}R_{11}$, C_{2-5} alkenyl, or C_{2-5} alkynyl;

R_4 is

a) C_{1-4} alkyl optionally substituted with one or more halos, OH, CN, $NR_{10}R_{11}$, or $-CO_2R_{13}$,

b) C_{2-4} alkenyl,

c) $-NR_{16}R_{18}$,

d) $-N_3$,

e) $-NHC(=O)R_7$,

f) $-NR_{20}C(=O)R_7$,

g) $-N(R_{19})_2$,

h) $-NR_{16}R_{19}$, or

i) $-NR_{19}R_{20}$,

R_5 and R_6 at each occurrence are the same or different and are

a) C_{1-2} alkyl, or

b) R_5 and R_6 taken together are $-(CH_2)_k-$;

R_7 is C_{1-4} alkyl optionally substituted with one or more halos;

R_8 is

a) H, or

b) C_{1-8} alkyl optionally substituted with one or more halos, or C_{3-8} cycloalkyl;

R_9 is C_{1-4} alkyl substituted with one or more

a) $-S(=O)R_{17}$,

b) $-OR_{13}$,

c) $-OC(=O)R_{13}$,

d) $-NR_{10}R_{11}$, or

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e) C_{1-5} alkenyl optionally substituted with CHO;

R_{10} and R_{11} at each occurrence are the same or different and are

a) H,

b) C_{1-4} alkyl, or

c) C_{3-8} cycloalkyl;

R_{12} is

a) $-NR_{10}R_{11}$,

b) $-OR_{10}$; or

c) $-NHC(=O)R_{10}$;

R_{13} is

a) H, or

b) C_{1-4} alkyl;

R_{14} and R_{15} at each occurrence are the same or different and are

a) C_{1-4} alkyl, or

b) R_{14} and R_{15} taken together are $-(CH)_l-$;

R_{16} is

a) H,

b) C_{1-4} alkyl, or

c) C_{3-8} cycloalkyl;

R_{17} is

a) C_{1-4} alkyl, or

b) C_{3-8} cycloalkyl;

R_{18} is

a) H,

b) C_{1-4} alkyl,

c) C_{2-4} alkenyl,

d) C_{3-4} cycloalkyl,

e) $-OR_{13}$ or

f) $-NR_{21}R_{22}$;

R_{19} is

a) Cl,

b) Br, or

c) I;

R_{20} is a physiologically acceptable cation;

R_{21} and R_{22} at each occurrence are the same or different and are

a) H,

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b) C_{1-4} alkyl, or

c) $-NR_{21}R_{22}$ taken together are $-(CH_2)_m-$;

wherein R_{23} and R_{24} at each occurrence are the same or different and are

a) H,

b) F,

c) Cl,

d) C_{1-2} alkyl,

e) CN

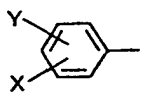
f) OH,

g) C_{1-2} alkoxy,

h) nitro, or

i) amino;

Q is

a) 

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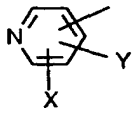
b) 

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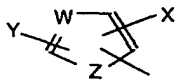
c) 

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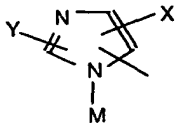
d) 

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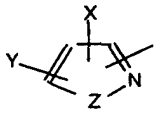
e) 

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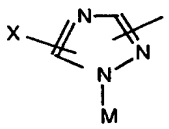
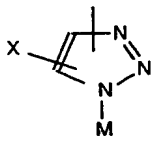
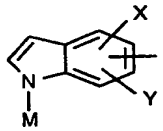
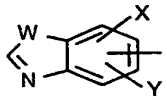
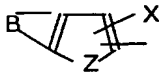
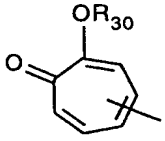
f)  ,

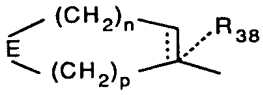
g)  ,

h)  ,

i)  ,

j) 

k)  ,

l)  ,

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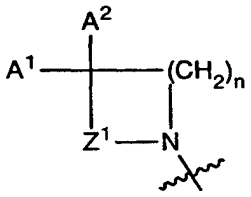
m) a diazinyl group optionally substituted with X and Y,

n) a triazinyl group optionally substituted with X and Y,

o) a quinolinyl group optionally substituted with X and Y,

p) a quinoxalinyl group optionally substituted with X and Y,

q) a naphthyridinyl group optionally substituted with X and Y,

r) 

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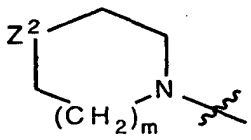
s) 

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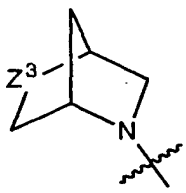
t) 

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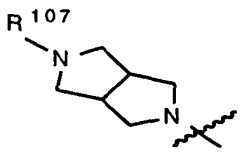
u) 

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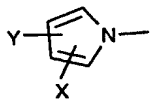
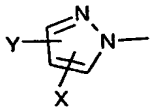
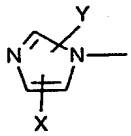
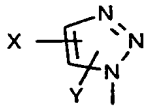
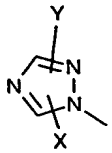
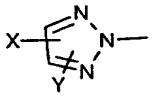
v)  ,

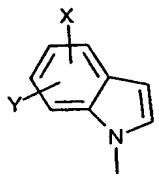
w)  ,

x)  ,

y)  ,

z)  ,

aa)  ,

bb)  or,

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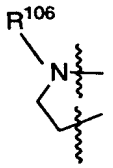
Q and R_{24} taken together are



wherein Z^1 is

a) $-CH_2-$,
b) $-CH(R^{104})-CH_2-$,
c) -C(O)-, or
d) $-CH_2CH_2CH_2-$;

wherein Z^2 is

a) $-O_2S-$,
b) -O-,
c) $-N(R^{107})-$,
d) -OS-, or
e) -S-;

wherein Z^3 is

a) $-O_2S-$,
b) -O-,
c) -OS-, or
d) -S-;

wherein A^1 is

a) H-, or
b) CH_3;

wherein A^2 is

a) H-,
b) HO-,
c) CH_3-,
d) CH_3O-,
e) $R^{102}O-CH_2-C(O)-NH-$
f) $R^{103}O-C(O)-NH-$,
g) (C_1-C_2)alkyl-O-C(O)-,
h) $HO-CH_2-$,
i) CH_3O-NH-,
j) (C_1-C_3)alkyl-O_2C-

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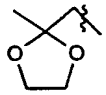
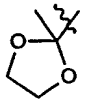
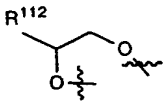
k) CH_3-C(O)-,

l) CH_3-C(O)-CH_2-,

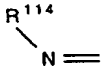
m)  , or

n)  ,

A^1 and A^2 taken together are:

a)  ,

b) O= , or

c)  ;

wherein R^{102} is

a) H-,

b) CH_3-,

c) phenyl-CH_2-, or

d) $CH_3C(O)$-;

wherein R^{103} is

a) (C_1-C_3)alkyl-, or

b) phenyl-;

wherein R^{104} is

a) H-, or

b) HO-;

wherein R^{105} is

a) H-,

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b) $(C_1\text{-}C_3)$alkyl-,

c) $CH_2 = CH\text{-}CH_2$-, or

d) $CH_3\text{-}O\text{-}(CH_2)_2$-;

wherein R^{106} is

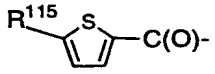
a) $CH_3\text{-}C(O)$-,

b) H-C(O)-,

c) $Cl_2CH\text{-}C(O)$-,

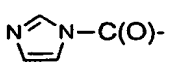
d) $HOCH_2\text{-}C(O)$-,

e) CH_3SO_2-,

f) 

,

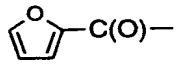
g) $F_2CHC(O)$-,

h) 

,

i) $H_3C\text{-}C(O)\text{-}O\text{-}CH_2\text{-}C(O)$-,

j) $H\text{-}C(O)\text{-}O\text{-}CH_2\text{-}C(O)$-,

k) 

,

l) $HC{\equiv}C\text{-}CH_2O\text{-}CH_2\text{-}C(O)$-, or

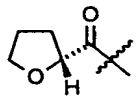
m) phenyl-$CH_2\text{-}O\text{-}CH_2\text{-}C(O)$-;

wherein R^{107} is

a) $R^{102}O\text{-}C(R^{110})(R^{111})\text{-}C(O)$-,

b) $R^{103}O\text{-}C(O)$-,

c) $R^{108}\text{-}C(O)$-,

d) 

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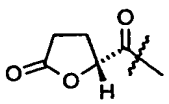
e) 

,

f) $H_3C\text{-}C(O)\text{-}(CH_2)_2\text{-}C(O)$-,

g) $R^{109}\text{-}SO_2$-,

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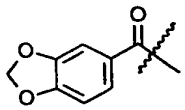
h)  ,

i) $HO\text{-}CH_2\text{-}C(O)\text{-}$,

j) $R^{116}\text{-}(CH_2)_2\text{-}$,

k) $R^{113}\text{-}C(O)\text{-}O\text{-}CH_2\text{-}C(O)\text{-}$,

l) $(CH_3)_2N\text{-}CH_2\text{-}C(O)\text{-}NH\text{-}$,

m) $NC\text{-}CH_2\text{-}$, or

n) $F_2\text{-}CH\text{-}CH_2\text{-}$;

wherein R^{108} is

a) H-,

b) $(C_1\text{-}C_4)$alkyl,

c) aryl $\text{-}(CH_2)_p$,

d) $ClH_2C\text{-}$,

e) $Cl_2HC\text{-}$,

f) $FH_2C\text{-}$,

g) $F_2HC\text{-}$, or

h) $(C_3\text{-}C_6)$cycloalkyl;

wherein R^{109} is

a) $\text{-}CH_3$,

b) $\text{-}CH_2Cl$

c) $\text{-}CH_2CH{=}CH_2$,

d) aryl, or

e) $\text{-}CH_2CN$;

wherein R^{110} and R^{111} are independently

a) H-,

b) $CH_3\text{-}$; or

wherein R^{112} is

a) H-,

b) $CH_3O\text{-}CH_2O\text{-}CH_2\text{-}$, or

c) $HOCH_2\text{-}$;

wherein R^{113} is

a) $CH_3\text{-}$,

b) $HOCH_2\text{-}$,

c) $(CH_3)_2N$-phenyl, or

d) $(CH_3)_2N\text{-}CH_2\text{-}$;

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wherein R^{114} is

a) HO-,

b) CH_3O-,

c) H_2N-,

d) CH_3O-C(O)-O-,

e) CH_3-C(O)-O-CH_2-C(O)-O-,

f) phenyl-CH_2-O-CH_2-C(O)-O-,

g) HO-$(CH_2)_2$-O-,

h) CH_3O-CH_2-O-$(CH_2)_2$-O-, or

i) CH_3O-CH_2-O-;wherein R^{113} is

a) CH_3-,

b) $HOCH_2$-,

c) $(CH_3)_2N$-phenyl, or

d) $(CH_3)_2N$-CH_2-;

wherein R^{115} is

a) H-, or

b) Cl-;

wherein R^{116} is

a) HO-

b) CH_3O-, or

c) F;

B is an unsaturated 4-atom linker having one nitrogen and three carbons;

M is

a) H,

b) C_{1-8} alkyl,

c) C_{3-8} cycloalkyl,

d) -$(CH_2)_m$$OR_{13}$, or

e) -$(CH_2)_h$-$NR_{21}R_{22}$;

Z is

a) O,

b) S, or

c) NM;

W is

a) CH,

b) N, or

c) S or O when Z is NM;

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Y is

a) H,
b) F,
c) Cl,
d) Br,
e) C_{1-3} alkyl, or
f) NO_2;

X is

a) H,
b) -CN,
c) OR_{27},
d) halo,
e) NO_2,
f) tetrazoyl,
g) -SH,
h) $-S(=O)_iR_4$,
i) $-S(=O)_2-N=S(O)_jR_5R_6$,
j) $-SC(=O)R_7$,
k) $-C(=O)R_{25}$,
l) $-C(=O)NR_{27}R_{28}$,
m) $-C(=NR_{29})R_{25}$,
n) $-C(R_{25})(R_{28})-OR_{13}$,
o) $-C(R_{25})(R_{28})-OC(=O)R_{13}$,
p) $-C(R_{28})(OR_{13})-(CH_2)_h-NR_{27}R_{28}$,
q) $-NR_{27}R_{28}$,
r) $-N(R_{27})C(=O)R_7$,
s) $-N(R_{27})-S(=O)_iR_7$,
t) $-C(OR_{14})(OR_{15})R_{28}$,
u) $-C(R_{25})(R_{16})-NR_{27}R_{26}$, or
v) C_{1-8} alkyl substituted with one or more halos, OH, =O other than at alpha position, $-S(=O)_iR_{17}$, $-NR_{27}R_{28}$, C_{2-5} alkenyl, C_{2-5} alkynyl, or C_{3-8} cycloalkyl;

R_4, R_5, R_6, R_7, R_{13}, R_{14}, R_{15}, R_{16}, and R_{17} are the same as defined above;

R_{25} is

a) H,
b) C_{1-8} alkyl optionally substituted with one or more halos, C_{3-8}

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cycloalkyl, C_{1-4} alkyl substituted with one or more of $-S(=O)_iR_{17}$, $-OR_{13}$, or $OC(=O)R_{13}$, $NR_{27}R_{28}$, or

c) C_{2-5} alkenyl optionally substituted with CHO, or CO_2R_{13};

R_{26} is

a) R_{28}, or

b) $NR_{27}N_{28}$;

R_{27} and R_{28} at each occurrence are the same or different and are

a) H,

b) C_{1-8} alkyl,

c) C_{3-8} cycloalkyl,

d) $-(CH_2)_mOR_{13}$,

e) $-(CH_2)_h-NR_{21}R_{22}$, or

f) R_{27} and R_{28} taken together are $-(CH_2)_2O(CH_2)_2-$, $-(CH_2)_hCH(COR_7)-$, or $-(CH_2)_2N(CH_2)_2(R_7)$;

R_{29} is

a) $-NR_{27}R_{28}$,

b) $-OR_{27}$, or

c) $-NHC(=O)R_{28}$;

wherein R_{30} is

a) H,

b) C_{1-8} alkyl optionally substituted with one or more halos, or

c) C_{1-8} alkyl optionally substituted with one or more OH, or C_{1-6} alkoxy;

wherein E is

a) NR_{39},

b) $-S(=O)_i$, or

c) O;

R_{38} is

a) H,

b) C_{1-6} alkyl,

c) $-(CH_2)_q$-aryl, or

d) halo;

R_{39} is

a) H,

b) C_{1-6} alkyl optionally substituted with one or more OH, halo, or -CN,

c) $-(CH_2)_q$-aryl,

d) $-CO_2R_{40}$,

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e) $-COR_{41}$,

f) $-C(=O)-(CH_2)_q-C(=O)R_{40}$,

g) $-S(=O)_2-C_{1-6}$ alkyl,

h) $-S(=O)_2-(CH_2)_q$-aryl, or

i) $-(C=O)_j$-Het;

R_{40} is

a) H,

b) C_{1-6} alkyl optionally substituted with one or more OH, halo, or -CN,

c) $-(CH_2)_q$-aryl, or

d) $-(CH_2)_q-OR_{42}$;

R_{41} is

a) C_{1-6} alkyl optionally substituted with one or more OH, halo, or -CN,

b) $-(CH_2)_q$-aryl, or

c) $-(CH_2)_q-OR_{42}$;

R_{42} is

a) H,

b) C_{1-6} alkyl,

c) $-(CH_2)_q$-aryl, or

d) $-C(=O)-C_{1-6}$ alkyl;

aryl is

a) phenyl,

b) pyridyl, or

c) napthyl; a to c optionally substituted with one or more halo, -CN, OH, SH, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} alkylthio;

wherein R_{43} is

a) H,

b) C_{1-2} alkyl,

c) F, or

d) OH;

R_{44} is

a) H,

b) CF_3,

c) C_{1-3} alkyl optionally substituted with one or more halo,

d) phenyl optionally substituted with one or more halo,

e) R_{44} and R_{45} taken together are a 5-, 6-, or 7-membered ring of the

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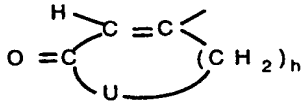
formula,

or 

f) R_{44} and R_{45} taken together are $-(CH_2)_k-$, when R_{46} is an electron-withdrawing group;

R_{45} and R_{46} at each occurrence are the same or different and are

a) an electron-withdrawing group,

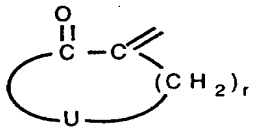
b) H,

c) CF_3,

d) C_{1-3} alkyl optionally substituted with one halo,

e) phenyl, provided at least one of R_{45} or R_{46} is an electron-withdrawing group, or

f) R_{45} and R_{46} taken together are a 5-, 6-, 7-membered ring of the formula

 ;

U is

a) CH_2,

b) O,

c) S, or

d) NR_{47};

R_{47} is

a) H, or

b) C_{1-5} alkyl;

wherein R_{48} is

a) carboxyl,

b) halo,

c) -CN,

d) mercapto,

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e) formyl,

f) CF_3,

g) $-NO_2$,

h) C_{1-6} alkoxy,

i) C_{1-6} alkoxycarbonyl,

j) C_{1-6} alkythio,

k) C_{1-6} acyl,

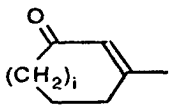
l) $-NR_{49}R_{50}$,

m) C_{1-6} alkyl optionally substituted with OH, C_{1-5} alkoxy, C_{1-5} acyl, or $-NR_{49}R_{50}$,

n) C_{2-8} alkenylphenyl optionally substituted with one or two R_{51},

o) phenyl optionally substituted with one or two R_{51},

p) a 5-, or 6-membered (un)saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with one or two R_{51}, or

q)  ;

R_{49} and R_{50} at each occurrence are the same or different and are

a) H,

b) C_{1-4} alkyl,

c) C_{5-6} cycloalkyl, or

d) R_{49} and R_{50} taken together with the nitrogen atom is a 5-, 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, and O, and can in turn be optionally substituted with, including on the further nitrogen atom, C_{1-3} alkyl, or C_{1-3} acyl;

R_{51} is

a) carboxyl,

b) halo,

c) -CN,

d) mercapto,

e) formyl,

f) CF_3,

g) $-NO_2$,

h) C_{1-6} alkoxy,

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i) C_{1-6} alkoxycarbonyl,
j) C_{1-6} alkythio,
k) C_{1-6} acyl,
l) C_{1-6} alkyl optionally substituted with OH, C_{1-5} alkoxy, C_{1-5} acyl, or $-NR_{49}R_{50}$,
m) phenyl,
n) $-C(=O)NR_{52}\ R_{53}$,
o) $-NR_{49}R_{50}$,
p) $-N(R_{52})(-SO_2R_{54})$,
q) $-SO_2-NR_{52}R_{53}$, or
r) $-S(=O)_iR_{54}$;

R_{52} and R_{53} at each occurrence are the same or different and are
a) H,
b) C_{1-6} alkyl, or
c) phenyl;

R_{54} is
a) C_{1-4} alkyl, or
b) phenyl optionally substituted with C_{1-4} alkyl;

wherein R_{55} is
a) carboxyl,
b) halo,
c) -CN,
d) mercapto,
e) formyl,
f) CF_3,
g) $-NO_2$,
h) C_{1-6} alkoxy,
i) C_{1-6} alkoxycarbonyl,
j) C_{1-6} alkythio
k) C_{1-6} acyl,
l) $-NR_{56}\ R_{57}$,
m) C_{1-6} alkyl optionally substituted with OH, C_{1-5} alkoxy, C_{1-5} acyl, or $-NR_{56}R_{57}$,
n) C_{2-8} alkenylphenyl optionally substituted with one or two R_{58},
o) phenyl optionally substituted with one or two R_{58},
p) a 5- or 6-membered (un)saturated heterocyclic moiety having one to

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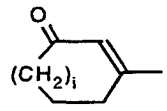
three atoms selected from the group consisting of S, N, and O, optionally substituted with one or two R_{58}, or

q)  ;

R_{56} and R_{57} at each occurrence are the same or different and are

a) H,

b) formyl,

c) C_{1-4} alkyl,

d) C_{1-4} acyl,

e) phenyl,

f) C_{3-6} cycloalkyl, or

g) R_{56} and R_{57} taken together with the nitrogen atom is a 5-, 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, and O, and can in turn be optionally substituted with, including on the further nitrogen atom, phenyl, pyrimidyl, C_{1-3} alkyl, or C_{1-3} acyl;

R_{58} is

a) carboxyl,

b) halo,

c) -CN,

d) mercapto,

e) formyl,

f) CF_3,

g) $-NO_2$,

h) C_{1-6} alkoxy,

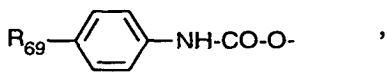
i) C_{1-6} alkoxycarbonyl,

j) C_{1-6} alkythio,

k) C_{1-6} acyl,

l) phenyl,

m) C_{1-6} alkyl optionally substituted with OH, azido, C_{1-5} alkoxy, C_{1-5} acyl, $-NR_{65}R_{66}$, $-SR_{67}$, $-O-SO_2R_{68}$, or



,

SUBSTITUTE SHEET (RULE 26)

n) $-C(=O)NR_{59}\ R_{60}$,

o) $-NR_{56}R_{57}$,

p) $-N(R_{59})(-SO_2R_{54})$,

q) $-SO_2-NR_{59}R_{60}$,

r) $-S(=O)_iR_{54}$,

s) $-CH=N-R_{61}$, or

t) $-CH(OH)-SO_3R_{64}$;

R_{54} is the same as defined above;

R_{59} and R_{60} at each occurrence are the same or different and are

a) H,

b) C_{1-6} alkyl,

c) phenyl, or

d) tolyl;

R_{61} is

a) OH,

b) benzyloxy,

c) $-NH-C(=O)-NH_2$,

d) $-NH-C(=S)-NH_2$, or

e) $-NH-C(=NH)-NR_{62}R_{63}$;

R_{62} and R_{63} at each occurrence are the same or different and are

a) H, or

b) C_{1-4} alkyl optionally substituted with phenyl or pyridyl;

R_{64} is

a) H, or

b) a sodium ion;

R_{65} and R_{66} at each occurrence are the same or different and are

a) H,

b) formyl,

c) C_{1-4} alkyl,

d) C_{1-4} acyl,

e) phenyl,

f) C_{3-6} cycloalkyl,

g) R_{65} and R_{66} taken together are a 5-, 6-membered saturated heterocyclic moiety having one to three atoms selected from the group consisting of

S, N, and O, optionally substituted with, including on the nitrogen

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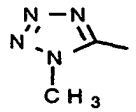
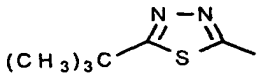
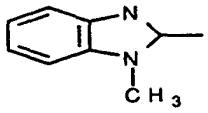
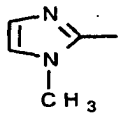
atom, phenyl, pyrimidyl, C_{1-3} alkyl, or C_{1-3} acyl,

h) $-P(O)(OR_{70})(OR_{71})$, or

i) $-SO_2-R_{72}$;

R_{67} is

R_{68} is C_{1-3} alkyl;

R_{69} is

a) C_{1-6} alkoxycarbonyl, or

b) carboxyl;

R_{70} and R_{71} at each occurrence are the same or different and are

a) H, or

b) C_{1-3} alkyl;

R_{72} is

a) methyl,

b) phenyl, or

c) tolyl;

wherein K is

a) O, or

b) S;

R_{73}, R_{74}, R_{75}, R_{76}, and R_{77} at each occurrence are the same or different and are

a) H,

b) carboxyl,

c) halo,

d) -CN,

e) mercapto,

f) formyl,

g) CF_3,

h) $-NO_2$,

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i) C_{1-6} alkoxy,

j) C_{1-6} alkoxycarbonyl,

k) C_{1-6} alkythio,

l) C_{1-6} acyl,

m) $-NR_{78}R_{79}$,

n) C_{1-6} alkyl optionally substituted with OH, C_{1-5} alkoxy, C_{1-5} acyl, $-NR_{78}R_{79}$, -N(phenyl)(CH_2-CH_2-OH), -O-CH(CH_3)(OCH_2CH_3), or -O-phenyl-[para-NHC(=O)CH_3],

o) C_{2-8} alkenylphenyl optionally substituted with R_{51},

p) phenyl optionally substituted with R_{51}, or

q) a 5-, or 6-membered (un)saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with R_{51};

R_{51} is the same as defined above;

R_{78} and R_{79} at each occurrence are the same or different and are

a) H,

b) C_{1-4} alkyl,

c) phenyl, or

d) R_{78} and R_{79} taken together with the nitrogen atom is a 5-, 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, and O, and can in turn be optionally substituted with, including on the further nitrogen atom, C_{1-3} alkyl, or C_{1-3} acyl;

wherein T is

a) O,

b) S, or

c) SO_2;

R_{75}, R_{76}, and R_{77} are the same as defined above;

R_{80} is

a) H,

b) formyl,

c) carboxyl,

d) C_{1-6} alkoxycarbonyl,

e) C_{1-8} alkyl,

f) C_{2-8} alkenyl,

wherein the substituents (e) and (f) can be optionally substituted with

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OH, halo, C_{1-6} alkoxy, C_{1-6} acyl, C_{1-6} alkylthio or C_{1-6} alkoxycarbonyl, or phenyl optionally substituted with halo,

g) an aromatic moiety having 6 to 10 carbon atoms optionally substituted with carboxyl, halo, -CN, formyl, CF_3, $-NO_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} acyl, C_{1-6} alkylthio, or C_{1-6} alkoxycarbonyl;

h) $-NR_{81}R_{82}$,

i) $-OR_{90}$,

j) $-S(=O)_i-R_{91}$,

k) $-SO_2-N(R_{92})(R_{93})$, or

l) a radical of the following formulas:

R_{81} and R_{82} at each occurrence are the same or different and are

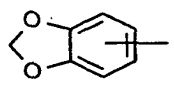
a) H,

b) C_{3-6} cycloalkyl,

c) phenyl,

d) C_{1-6} acyl,

e) C_{1-8} alkyl optionally substituted with OH, C_{1-6} alkoxy which can be substituted with OH, a 5-, or 6-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, phenyl optionally substituted with OH, CF_3, halo, $-NO_2$, C_{1-4} alkoxy, $-NR_{83}R_{84}$, or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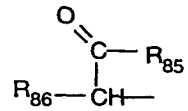
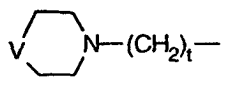
f) 
, or

g) 
;

V is

a) O,

b) CH_2, or

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c) NR_{87};

R_{83} and R_{84} at each occurrence are the same or different and are

a) H, or

b) C_{1-4} alkyl;

R_{85} is

a) OH,

b) C_{1-4} alkoxy, or

c) $-NR_{88}R_{89}$;

R_{86} is

a) H, or

b) C_{1-7} alkyl optionally substituted with indolyl, OH, mercaptyl, imidazoly, methylthio, amino, phenyl optionally substituted with OH, $-C(=O)-NH_2$, $-CO_2H$, or $-C(=NH)-NH_2$;

R_{87} is

a) H,

b) phenyl, or

c) C_{1-6} alkyl optionally substituted by OH;

R_{88} and R_{89} at each occurrence are the same or different and are

a) H,

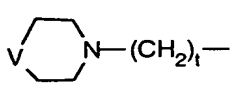
b) C_{1-5} alkyl

c) C_{3-6} cycloalky, or

d) phenyl;

R_{90} is

a) C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy or C_{1-6} hydroxy, C_{3-6} cycloalkyl, a 6-membered aromatic optionally benzo-fused heterocyclic moiety having one to three nitrogen atoms, which can in turn be substituted with one or two $-NO_2$, CF_3, halo, -CN, OH, C_{1-5} alkyl, C_{1-5} alkoxy, or C_{1-5} acyl;

b) 

,

c) phenyl, or

d) pyridyl;

R_{91} is

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a) C_{1-16} alkyl,

b) C_{2-16} alkenyl,

wherein the substituents (a) and (b) can be optionally substituted with C_{1-6} alkoxycarbonyl, or a 5-, 6-, 7-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,

c) an aromatic moiety having 6 to 10 carbon atoms, or

d) a 5-, 6-, 7-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,

wherein the substituents (c) and (d) can be optionally substituted with carboxyl, halo, -CN, formyl, CF_3, $-NO_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} acyl, C_{1-6} alkylthio, or C_{1-6} alkoxycarbonyl;

R_{92} and R_{93} at each occurrence are the same or different and are

a) H,

b) phenyl,

c) C_{1-6} alkyl, or

d) benzyl;

R_{94} and R_{95} at each occurrence are the same or different and are

a) H,

b) OH,

c) C_{1-6} alkyl optionally substituted with $-NR_{83}R_{84}$, or

d) R_{94} and R_{95} taken together are =O;

R_{96} is

a) an aromatic moiety having 6 to 10 carbon atoms,

b) a 5-, or 6-membered aromatic optionally benzo-fused heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,

wherein the substituents (a) and (b) which can in turn be substituted with one or three $-NO_2$, CF_3, halo, -CN, OH, phenyl, C_{1-5} alkyl, C_{1-5} alkoxy, or C_{1-5} acyl,

c) morpholinyl,

d) OH,

e) C_{1-6} alkoxy,

f) $-NR_{83}R_{84}$,

g) $-C(=O)-R_{97}$, or

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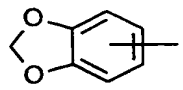
h)  ;

R_{97} is

a) morpholinyl,

b) OH, or

c) C_{1-6} alkoxy;

h is 1, 2, or 3;

i is 0, 1, or 2;

j is 0 or 1;

k is 3, 4, or 5;

l is 2 or 3;

m is 4 or 5;

n is 0, 1, 2, 3, 4, or 5;

p is 0, 1, 2, 3, 4, or 5; with the proviso that n and p together are 1, 2, 3, 4, or 5;

q is 1, 2, 3, or 4;

r is 2, 3, or 4;

t is 0, 1, 2, 3, 4, 5, or 6;

u is 1 or 2.

DETAILED DESCRIPTION OF THE INVENTION

The new compounds of the invention can be prepared using known compounds and intermediates of oxzolidinones, isoxazolines and butyolactones as intermediates and synthetic methods known in the art. Thioamides of the invention can typically be prepared by the reaction of the corresponding amide with Lawesson's reagent.

Compounds disclosed in the following publications are suitable intermediates for preparation of the compounds of this invention and are hereby incorporated by reference for their disclosure of suitable compounds that can be converted to the subject thiocarbonyl derivatives.

U.S. Patents 5,225,565; 5,182,403; 5,164,510; 5,247,090; 5,231,188; 5,565,571; 5,547,950; and 5,523,403.

PCT Application and publications PCT/US93/04850, WO94/01110; PCT/US94/08904, WO95/07271; PCT/US95/02972, WO95/25106; PCT/US95/10992, WO96/13502; PCT/US96/05202, WO96/35691; PCT/US96/12766; PCT/US96/13726;

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PCT/US96/14135; PCT/US96/17120; PCT/US96/19149; PCT/US97/01970; PCT/US95/12751, WO96/15130; and PCT/US96/00718, WO96/23788.

Chemical conversion techniques for converting various intermediates having a CH_2NH_2 on the oxazolidinone ring to CH_2NH-C(S)-CH_3 is disclosed by Hartke, K., Barrmeyer, S., J. prakt. Chem. 1996, 338, 251-6. Similarly, conversion of $CH_2NHC(=0)CH_3$ to $CH_2NHC(S)NHCH_3$ is reported by Cava, M.P.; Levinson, M.I., Thionation Reactions of Lawesson's Reagents, Tetrahedron 1985, 41, 5061-87.

For the purpose of the present invention, the carbon content of various hydrocarbon containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_{i-j} defines the number of carbon atoms present from the integer "i" to the integer "j", inclusive. Thus, C_{1-4} alkyl refers to alkyl of 1-4 carbon atoms, inclusive, or methyl, ethyl, propyl, butyl and isomeric forms thereof.

The terms "C_{1-2} alkyl", "C_{1-3} alkyl", "C_{1-4} alkyl", "C_{1-5} alkyl", "C_{1-6} alkyl", "C_{1-8} alkyl", and "C_{1-16} alkyl" refer to an alkyl group having one to two, one to three, one to four, one to five, one to six, one to eight, or one to sixteen carbon atoms respectively such as, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl and their isomeric forms thereof.

The terms "C_{2-4} alkenyl", "C_{2-5} alkenyl", "C_{2-8} alkenyl", "C_{2-14} alkenyl" and "C_{2-16} alkenyl" refer to at least one double bond alkenyl group having two to four, two to five, two to eight, two to fourteen, or two to sixteen carbon atoms, respectively such as, for example, ethenyl, propenyl, butenyl, pentenyl, pentdienyl, hexenyl, hexdienyl, heptenyl, heptdienyl, octenyl, octdienyl, octatrienyl, nonenyl, nonedienyl, nonatrienyl, undecenyl, undecdienyl, dodecenyl, tridecenyl, tetradecenyl and their isomeric forms thereof.

The terms "C_{2-5} alkynyl", "C_{2-8} alkynyl", and "C_{2-10} alkynyl" refer to at least one triple bond alkynyl group having two to five, two to eight, or two to ten carbon atoms respectively such as, for example, ethynyl, propynyl, butynyl, pentynyl, pentdiynyl, hexynyl, hexdiynyl, heptynyl, heptdiynyl, octynyl, octdiynyl, octatriynyl, nonynyl, nonediynyl, nonatriynyl and their isomeric forms thereof.

The terms "C_{3-4} cycloalkyl", "C_{3-6} cycloalkyl", "C_{5-6} cycloalkyl", and "C_{3-8} cycloalkyl" refer to a cycloalkyl having three to four, three to six, five to six, or three to eight carbon atoms respectively such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and their isomeric forms thereof.

The terms "C_{1-4} alkoxy", "C_{1-6} alkoxy", and "C_{1-8} alkoxy" refer to an alkyl

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group having one to four, one to six, or one to eight carbon atoms respectively attached to an oxygen atom such as, for example, methoxy, ethoxy, propyloxy, butyloxy, pentyloxy, hexyloxy, heptyloxy, or octyloxy and their isomeric forms thereof.

The terms "C_{1-6} alkylamino", and "C_{1-8} alkylamino" refer to an alkyl group having one to six, or one to eight carbon atoms respectively attached to an amino moiety such as, for example, methylamino, ethylamino, propylamino, butylamino, pentylamino, hexylamino, heptylamino, or octoylamino and their isomeric forms thereof.

The terms "C_{1-6} dialkylamino", and "C_{1-8} dialkylamino" refer to two alkyl groups having one to six, or one to eight carbon atoms respectively attached to an amino moiety such as, for example, dimethylamino, methylethylamino, diethylamino, dipropylamino, methypropylamino, ethylpropylamino, dibutylamino, dipentylamino, dihexylamino, methylhecylamino, diheptylamino, or dioctoylamino and their isomeric forms thereof.

The terms "C_{1-3} acyl", "C_{1-4} acyl", "C_{1-5} acyl", "C_{1-6} acyl", "C_{1-8} acyl", and "C_{2-8} acyl" refer to a carbonyl group having an alkyl group of one to three, one to four, one to five, one to six, one to eight, or two to eight carbon atoms.

The terms "C_{1-4} alkoxycarbonyl", "C_{1-6} alkoxycarbonyl", and "C_{1-8} alkoxycarbonyl" refer to an ester group having an alkyl group of one to four, one to six, or one to eight carbon atoms.

The term "C_{1-8} alkyl phenyl" refers to an alkyl group having one to eight carbon atoms and isomeric forms thereof which is substituted with at least one phenyl radical.

The term "C_{2-8} alkenyl phenyl" refers to a at least one double bond alkenyl group having one to eight carbon atoms and isomeric forms thereof which is substituted with at least one phenyl radical.

The term "C_{1-8} alkyl pyridyl" refers to an alkyl group having one to eight carbon atoms and isomeric forms thereof which is substituted with at least one pyridyl radical.

The term "C_{1-8} hydroxyl" refers to an alkyl group having one to eight carbon atoms and isomeric forms thereof attached to a hydroxy group.

The term "C_{1-8} alkylsulfonyl" refers to an alkyl group having one to eight carbon atoms and isomeric forms thereof attached to a SO_2 moiety.

The term "C_{1-6} alkylthio" refers to an alkyl group having one to six carbon atoms and isomeric forms thereof attached to a sulfur atom.

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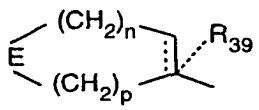
The term "Het" refers to 5 to 10 membered saturated, unsaturated or aromatic heterocyclic rings containing one or more oxygen, nitrogen, and sulfur forming such groups as, for example, pyridine, thiophene, furan, pyrazoline, pyrimidine, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 3-pyrazinyl, 2-quinolyl, 3-quinolyl, 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 2-quinazolinyl, 4-quinazolinyl, 2-quinoxalinyl, 1-phthalazinyl, 4-oxo-2-imidazolyl, 2-imidazolyl, 4-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 4-oxo-2-oxazolyl, 5-oxazolyl, 4,5,-dihydrooxazole, 1,2,3-oxathiole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isothiazole, 4-isothiazole, 5-isothiazole, 2-indolyl, 3-indolyl, 3-indazolyl, 2-benzoxazolyl, 2-benzothiazolyl, 2-benzimidazolyl, 2-benzofuranyl, 3-benzofuranyl, benzoisothiazole, benzisoxazole, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl, 3-isopyrrolyl, 4-isopyrrolyl, 5-isopyrrolyl, 1,2,3,-oxathiazole-1-oxide, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 5-oxo-1,2,4-oxadiazol-3-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 3-oxo-1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-5-yl, 2-oxo-1,3,4-thiadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,2,3,4-tetrazol-5-yl, 5-oxazolyl, 1-pyrrolyl, 1-pyrazolyl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, 1-tetrazolyl, 1-indolyl, 1-indazolyl, 2-isoindolyl, 7-oxo-2-isoindolyl,1-purinyl, 3-isothiazolyl, 4-isothiazolyl and 5-isothiazolyl, 1,3,4,-oxadiazole, 4-oxo-2-thiazolinyl, or 5-methyl-1,3,4-thiadiazol-2-yl, thiazoledione, 1,2,3,4-thiatriazole, 1,2,4-dithiazolone. Each of these moieties may be substituted as appropriate.

The term halo refers to fluoro, chloro, bromo, or iodo.

The compounds of the present invention can be converted to their salts, where appropriate, according to conventional methods.

The term "pharmaceutically acceptable salts" refers to acid addition salts useful for administering the compounds of this invention and include hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, lactate, mesylate, maleate, malate, succinate, tartrate, citric acid, 2-hydroxyethyl sulfonate, fumarate and the like. These salts may be in hydrated form.

When Q is the structure of



the dotted line in the heterocyclic ring means that this bond can be either single or double. In the case where the dotted line is a double bond, the R_{39} group will not be

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present.

The compounds of Formula I of this invention contain a chiral center at C5 of the isoxazoline ring, and as such there exist two enantiomers or a racemic mixture of both. This invention relates to both the enantiomers, as well as mixtures containing both the isomers. In addition, depending on substituents, additional chiral centers and other isomeric forms may be present in any of A or R_1 group, and this invention embraces all possible stereoisomers and geometric forms in these groups.

The compounds of this invention are useful for treatment of microbial infections in humans and other warm blooded animals, under both parenteral and oral administration.

The pharmaceutical compositions of this invention may be prepared by combining the compounds of this invention with a solid or liquid pharmaceutically acceptable carrier and, optionally, with pharmaceutically acceptable adjuvants and excipients employing standard and conventional techniques. Solid form compositions include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be at least one substance which may also function as a diluent, flavoring agent, solubilizer, lubricant, suspending agent, binder, tablet disintegrating agent, and encapsulating agent. Inert solid carriers include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, cellulosic materials, low melting wax, cocoa butter, and the like. Liquid form compositions include solutions, suspensions and emulsions. For example, there may be provided solutions of the compounds of this invention dissolved in water and water-propylene glycol and water-polyethylene glycol systems, optionally containing suitable conventional coloring agents, flavoring agents, stabilizers and thickening agents.

Preferably, the pharmaceutical composition is provided employing conventional techniques in unit dosage form containing effective or appropriate amounts of the active component, that is, the compound according to this invention.

The quantity of active component, that is the compound according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application, the potency of the particular compound, the desired concentration. Generally, the quantity of active component will range between 0.5% to 90% by weight of the composition.

In therapeutic use for treating, or combatting, bacterial infections in warm-blooded animals, the compounds or pharmaceutical compositions thereof will be

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administered orally and/or parenterally at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level of active component in the animal undergoing treatment which will be antibacterially effective. Generally, such antibacterially effective amount of dosage of active component will be in the range of about 0.1 to about 100, more preferably about 3.0 to about 50 mg/kg of body weight/day. It is to be understood that the dosages may vary depending upon the requirements of the patient, the severity of the bacterial infection being treated, and the particular compound being used. Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired blood-level or the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administration, e.g., 2-4 four times per day.

When the compounds according to this invention are administered parenterally, i.e., by injection, for example, by intravenous injection or by other parenteral routes of administration. Pharmaceutical compositions for parenteral administration will generally contain a pharmaceutically acceptable amount of the compound or a soluble salt (acid addition salt or base salt) dissolved in a pharmaceutically acceptable liquid carrier such as, for example, water-for-injection and a buffer to provide a suitably buffered isotonic solution, for example, having a pH of about 3.5-6. Suitable buffering agents include, for example, trisodium orthophosphate, sodium bicarbonate, sodium citrate, N-methylglucamine, L(+)-lysine and L(+)-arginine to name but a few representative buffering agents. The compound of this invention generally will be dissolved in the carrier in an amount sufficient to provide a pharmaceutically acceptable injectable concentration in the range of about 1 mg/mL to about 400 mg/mL of solution. The resulting liquid pharmaceutical composition will be administered so as to obtain the above-mentioned antibacterially effective amount of dosage. The compounds according to this invention are advantageously administered orally in solid and liquid dosage forms.

MIC Test Method

The in vitro MICs of test compounds were determined by a standard agar dilution method. A stock drug solution of each analog is prepared in the preferred solvent, usually DMSO:H_2O (1:3). Serial 2-fold dilutions of each sample are made using 1.0 ml aliquots of sterile distilled water. To each 1.0 ml aliquot of drug is added 9 ml of molten Mueller Hinton agar medium. The drug-supplemented agar is mixed, poured into 15 x 100 mm petri dishes, and allowed to solidify and dry prior to

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inoculation.

Vials of each of the test organisms are maintained frozen in the vapor phase of a liquid nitrogen freezer. Test cultures are grown overnight at 35°C on the medium appropriate for the organism. Colonies are harvested with a sterile swab, and cell suspensions are prepared in Trypticase Soy broth (TSB) to equal the turbidity of a 0.5 McFarland standard. A 1:20 dilution of each suspension is made in TSB. The plates containing the drug supplemented agar are inoculated with a 0.001 ml drop of the cell suspension using a Steers replicator, yielding approximately 10^4 to 10^5 cells per spot. The plates are incubated overnight at 35°C.

Following incubation the Minimum Inhibitory Concentration (MIC µg/ml), the lowest concentration of drug that inhibits visible growth of the organism, is read and recorded. The data is shown in Tables I and II.

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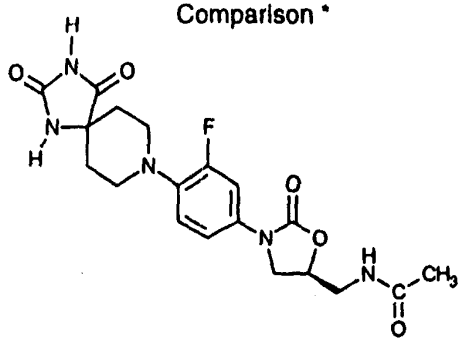
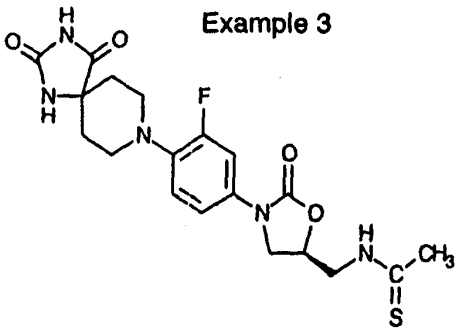
TABLE 1

Structure	Oxazolidinone MIC Values (Gram+)				
	SAUR 9213	SEPI 12084	EFAE 9217	SPNE 9912	SPYO 152
Comparison * 	16	4	8	.5	1
Example 3 	4	1	2	.25	.5

*not a compound of the subject invention

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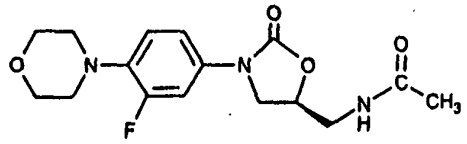
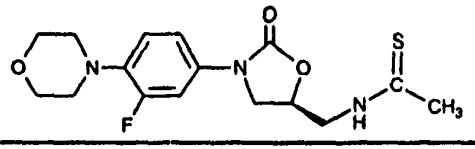
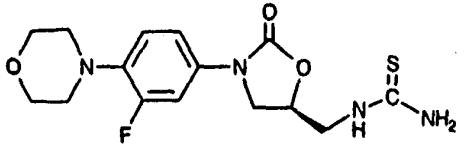
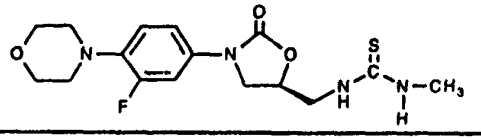
TABLE 1 (cont'd)

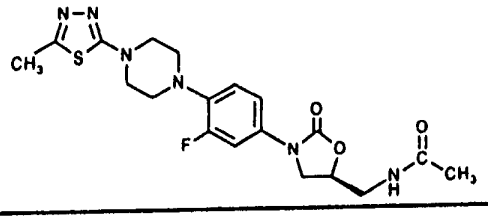
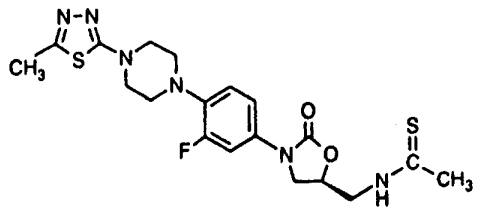
Structure	Oxazolidinone MIC Values (Gram+)				
	SAUR 9213	SEPI 12084	EFAE 9217	SPNE 9912	SPYO 152
Comparison * 	2	1	2	.5	1
Example 1 	1	.25	.5	.13	.13
Example 5 	1	.25	.5	<.125	.25
Example 6 	2	1	2	.5	1

*not a compound of the subject invention

SUBSTITUTE SHEET (RULE 26)

BNSDOCID: <WO__9854161A1_IA>

TABLE 1 (cont'd)

Structure	Oxazolidinone MIC Values (Gram+)				
	SAUR 9213	SEPI 12084	EFAE 9217	SPNE 9912	SPYO 152
Comparison * 	.5	.25	1	.13	.25
Example 2 	8	2	4	2	4

SAUR: S. *aureus*
SEPI: S. *epidermidis*
EFAE: E. *faecalis*
SPNE: S. *pneumoniae*
SPYO: S. *pyogenes*

*not a compound of the subject invention

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TABLE II

Example No.	SAUR 9213 MIC	SEPI 30593 MIC	EFAE 12712 MIC	SPNE 9912 MIC	SPYO 152 MIC	HINF 30063 MIC	MCAT 30610 MIC	EFAE 9217 MIC
1	1	0.25	0.5	<0.125	<0.125	8	1	0.5
2	8	4	8	2	4	>16	>16	4
3	4	1	1	0.25	0.5	16	4	2
5	1	0.5	0.5	<0.125	0.25	4	2	0.5
6	2	2	2	0.5	1	16	8	2
7	0.5	0.25	0.5	<0.125	0.25	4	1	0.5
8	2	1	0.5	<0.125	0.25	4	2	1
9	0.5	0.25	0.25	<0.125	<0.125	2	0.5	0.25
10	2	1	0.5	<0.125	0.25	2	1	1
11	0.25	0.25	0.25	<0.125	0.25	2	1	0.25
12	1	0.5	0.25	<0.125	<0.125	1	0.5	0.5
13	1	1	2	0.5	1	>16	8	2
14	1	0.5	1	0.25	0.5	8	1	1
15	32	16	32	4	8	>64	64	32
16	8	8	16	2	8	>64	32	16
17	2	2	4	1	2	64	16	4
18	2	1	2	<0.5	1	32	4	2
19	32	16	32	16	16	64	32	32
21	4	4	8	2	4	64	16	8
22, 23	0.5	0.5	1	<0.125	0.25	4	2	1
24	1	0.25	0.5	<0.125	0.25	4	2	0.5
25	0.5	0.25	0.5	<0.125	<0.125	2	2	0.5
26	1	0.5	1	0.25	0.5	16	2	1

TABLE II (cont'd)

Example No.	SAUR 9213 MIC	SEPI 30593 MIC	EFAE 12712 MIC	SPNE 9912 MIC	SPYO 152 MIC	HINF 30063 MIC	MCAT 30610 MIC	EFAE 9217 MIC
27	0.5	0.5	0.5	<0.125	0.25	4	2	1
28	0.5	0.25	0.5	0.25	0.25	2	1	0.5
29	0.25	0.25	0.25	<0.125	<0.125	2	0.5	0.25
30	4	1	0.5	<0.125	0.25	8	2	1
31	2	1	1	<0.125	0.25	4	1	1
32	16	2	2	0.25	0.25	8	2	4
33	4	2	1	0.25	0.25	4	2	4
34	2	1	2	0.5	1	>16	4	2
35	1	0.5	1	0.25	0.5	16	2	1

Key:

SAUR	9213:	S. *aureus*
SEPI	30593:	S. *epidermidis*
EFAE	12712:	E. *Faecium*
SPNE	9912:	S. *pneumoniae*
SPYO	152:	S. *pyogenes*
HINF	30063:	*Haemophilus influenzae*
MCAT	30610:	*Moraxella catarrhalis*
EFAE	9217:	*Enterococcus faecalis*

As shown in Scheme 1, the intermediates **II** for the compounds of this invention are also intermediates disclosed in the oxazolidinone patents and published applications hereinabove incorporated by reference. The intermediates **IV** for this invention are final products (Examples) from the oxazolidinone patents and published applications hereinabove incorporated by reference.

As shown in Scheme 1, Step 1, and illustrated in Example 5, the isothiocyanates **III** can be conveniently prepared by allowing the amine intermediates (**II**) to react with 1,1'-thiocarbonyldi-2(1H)-pyridone in solvents such as methylene chloride at 0 to 25°C. The thioureas (**Ia**, R' = H, $alkyl_{1-4}$) can then be prepared as shown in Step 2 by the reaction of **III** with ammonia or the appropriate primary amines in solvents such as 1,4-dioxane or tetrahydrofuran at 0-50°C. Alternatively, as illustrated in Example 6 and shown in Step 3, the thioureas can be prepared by allowing **II** to react with an appropriate isothiocyanate (R' - N = C = S) in solvents such as tetrahydrofuran at 0-50°C. Thioamides (**Ib**, R" = H, $alkyl_{1-4}$) are prepared by allowing **II** to react with an appropriate dithioester (R"' S-C(=S)-R", Step 4 as illustrated in Example 4. This reaction is carried out in aqueous-alcoholic solvents at 0-50°C in the presence of an equivalent of an alkali metal hydroxide. This reaction, especially when R"' is methyl or ethyl, can be catalyzed by an alkali metal fluoride.

The reaction of II with R"'-S-C(S)-R"' (R"'=CH_3, C_2H_5) to give Ib (Step 4) can also be carried out in the presence of a tertiary amine base such as triethylamine in solvents such as THF, dioxane or methylene chloride at 10-50°C for 3-48 hr.

When the reaction conditions are tolerated by the substituents on R (see, for example, Examples 1-3) the thioamides (**Ib**, R" - H, $alkyl_{1-4}$) can also be conveniently prepared (Step 5) by allowing the appropriate amide intermediates (IV) to react with reagents such as 2,4-bis(p-methoxyphenyl)-1,3-dithiadiphosphetane-2,4-disulfide (Lawesson's Reagent) in 1,4-dioxane, benzene, toluene or tetrahydrofuran at 60-110°C; phosphorus decasulfide and sodium carbonate in tetrahydrofuran at 20-50°C [Brillon, D., Synthetic Communications, 20, 3085 (1990)] or phosphorus decasulfide and sodium fluoride in 1,2-dimethoxyethane at 20-50°C [Hartke, K., Gerber, H.-D., J. Prakt. Chem., 338, 763 (1996)].

Compounds Ic are prepared (Step 6) by allowing II to react first with carbon disulfide and a tertiary amine base such as triethylamine in solvent mixtures containing water and methanol, ethanol or isopropanol at 10-50°C for 5-24 hours. The resulting intermediate is treated with an alkylating agent (R"" X where X represents bromo, iodo, alkylsulfonyloxy or arylsulfonyloxy) at 0-30°C to give

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compounds Ic. In Step 7, compounds Ic are allowed to react with alkali metal alkoxide such as sodium methoxide or potassium ethoxide in the corresponding alkanol as solvent. This reaction is conveniently carried out at the reflux temperature of the alkanol for 1-24 hr.

5

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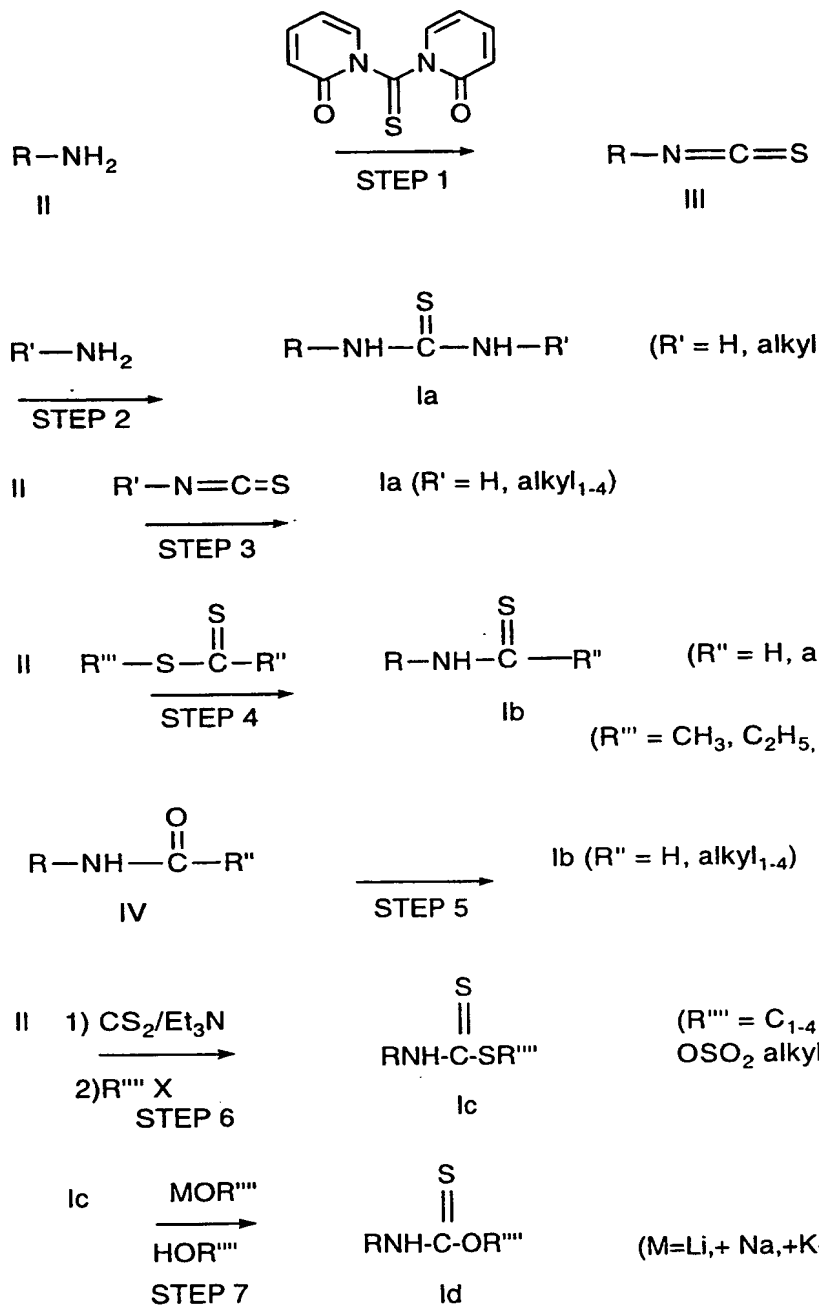
SCHEME 1



In order to more fully illustrate the nature of the invention and the manner of practicing the same, the following experimental examples are presented.

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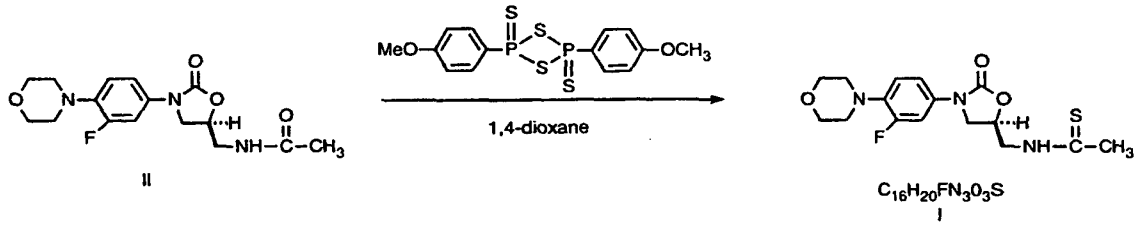
EXAMPLE 1: (*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (I)

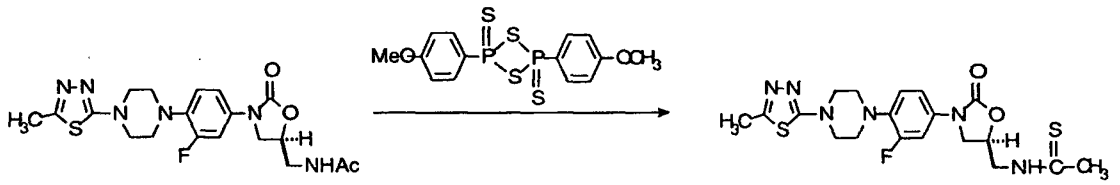


II

$C_{16}H_{20}FN_3O_3S$
I

A stirred mixture of II (PCT/US94/08904, 3.37 g, 10.0 mmol) in dry dioxane (100 mL), under nitrogen was treated with Lawesson's Reagent (4.04g, 10.0 mml), warmed to reflux during 1 h and refluxed for 1.5 h. The reaction was complete by TLC on silica gel with 10% MeOH-$CHCl_3$. It was kept at ambient temperature for 18 h and concentrated in vacuo. Chromatography of the residue on silica gel with mixtures of acetone-methylene chloride containing 10-15% acetone gave the product which was crystallized from acetone-hexane to give 1: mp 157.5-158.5 °C; HRMS theory for $C_{16}H_{20}FN_3O_3S$ (M^+): 353.1209; found: 353.1212. Anal. calcd for $C_{16}H_{20}FN_3O_3S$: C, 54.38; H, 5.38; N, 11.89; S, 9.07. Found: C, 54.21; H, 5.58; N, 11.78; S, 8.93.

EXAMPLE 2: (*S*)-N-[[3-[3-Fluoro-4-[4-(5-methyl-1,3,4-thiadiazol-2-yl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (2)



21

$C_{19}H_{23}FN_6O_2S_2$
2

According to Example 1, for the preparation of 1, 21 (PCT/US97/01970) was allowed to react with Lawesson's Reagent in refluxing dioxane to give 2: mp 222-223 °C; HRMS theory for $C_{19}H_{24}FN_6O_2S_2$ ($M+H^+$): 451.1386; found 451.1381.

EXAMPLE 3: (*S*)-N-[[3-[3-Fluoro-4-[2',5'-dioxospiro[piperidine-4,4'-imidazolidine]-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (3).

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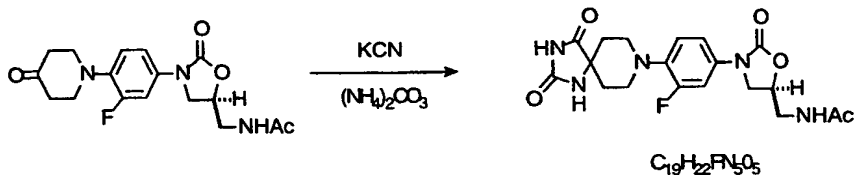
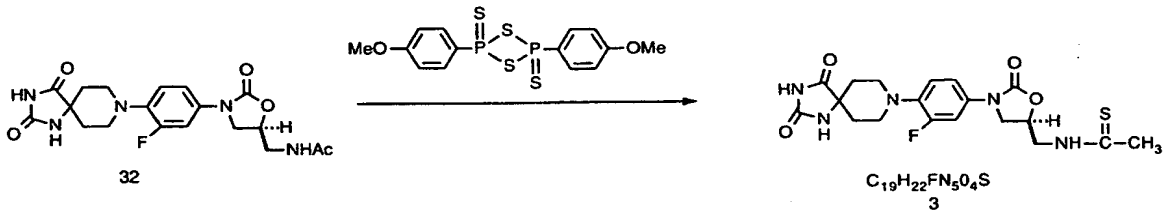
STEP A: (*S*)-N-[[3-[3-Fluoro-4-[2′,5′-dioxospiro[piperidine-4,4′-imidazolidine]-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (32).



31 $C_{19}H_{22}FN_5O_5$ 32

A stirred suspension of 31 (Case 4780.P CP, 0.349 g, 1.00 mmol) in 1:1 EtOH:H_2O (5 mL), under nitrogen, was treated with potassium cyanide (0.130 g, 2.00 mmol) and ammonium carbonate (0.701 g, 7.30 mmol), warmed at 55-60 °C for 5 h 15 min and kept at ambient temperature for 17 h 15 min. It was then chromatographed on silica gel with mixtures of MeOH-NH_4OH-$CHCl_3$ containing 5-20% MeOH and 0.5% NH_4OH to give 0.280 g of 32: HRMS calcd for $C_{19}H_{22}FN_5O_5$: 419.1605 (M^+); found 419.1613; Anal. calcd for $C_{19}H_{22}FN_5O_5 \cdot 1\ H_2O$: C, 52.17; H, 5.53; N, 16.01. Found: C, 52.44; H, 5.30; N, 16.11.

STEP B: (*S*)-N-[[3-[3-Fluoro-4-[2′,5′-dioxospiro[piperidine-4,4′-imidazolidine]-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (3).



32 $C_{19}H_{22}FN_5O_4S$ 3

A stirred suspension of 32 (0.210 g, 0.500 mmol) in dioxane (5.0 mL), under nitrogen was treated with Lawesson's Reagent (0.202 g, 0.500 mmol), refluxed for 4 h and concentrated in vacuo. The residue was chromatographed on silica gel with mixtures of MeOH-NH_4OH-$CHCl_3$ containing 1-10% MeOH and 0.1-0.5% NH_4OH and the resulting product was crystallized from MeOH-$CHCl_3$-EtOAc to give 0.0491 g of 3: mp 218.5 °C; HR FAB MS theory for $C_{19}H_{22}FN_5O_4S$ (M^+): 435.1376; found 435.1370. Anal. calcd for $C_{19}H_{22}FN_5O_4S \cdot 0.5\ H_2O$: C, 51.34; H, 5.21; N, 15.76. Found: C, 51.69; H, 5.00; N, 15.25.

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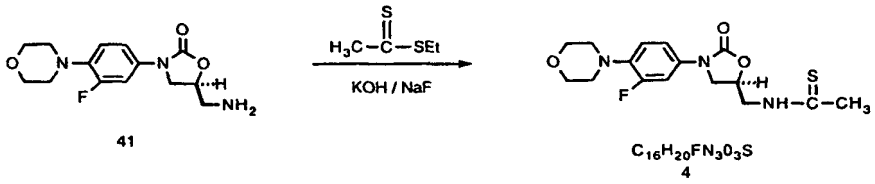
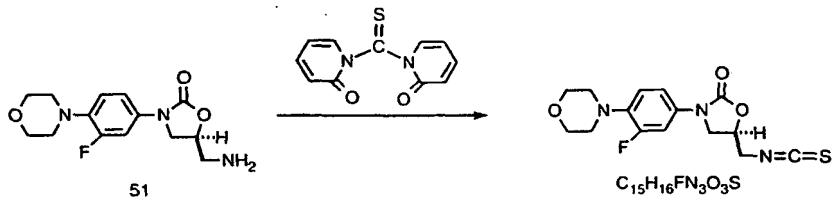
EXAMPLE 4: (*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (4).



A solution of 41 (148 mg, 0.500 mmol) and 0.97 M KOH (0.515 mL) in absolute EtOH (5 mL) was added to a solution of ethyl dithioacetate (57 μL, 0.50 mmol) and sodium fluoride (20 mg, 0.47 mmol) in absolute EtOH (5 mL) and the mixture was kept at ambient temperature for 3 h 40 min. Additional ethyl dithioacetate (5 μL) was added after 1 h 55 min and additional 0.97 M KOH (40 mL) and sodium fluoride (6 mg) were added to the mixture after 3h 5 min. The reaction was followed by TLC on silica gel with 10% MeOH-$CHCl_3$ and 30% acetone-CH_2Cl_2. The major product had an R_f on TLC that was the same as that of 4.

EXAMPLE 5: (*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea (5).

STEP A:



A solution of 51 (PCT/US94/08904, 2.07 g, 7.00 mmol) in CH_2Cl_2 was added, dropwise during 30 min, under nitrogen to an ice cold, stirred solution of 1,1′-thiocarbonyldi-2(1H)-pyridone (1.95 g, 8.40 mmol) in CH_2Cl_2 (70 mL). The mixture was warmed slowly to ambient temperature and kept for 18 h. It was then diluted with CH_2Cl_2, washed with water and aqueous NaCl, dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with 10% acetonitrile-CH_2Cl_2 gave 1.60 g of the isothiocyanate: HRMS theory for $C_{15}H_{16}FN_3O_3S$ (M^+): 337.0896; found

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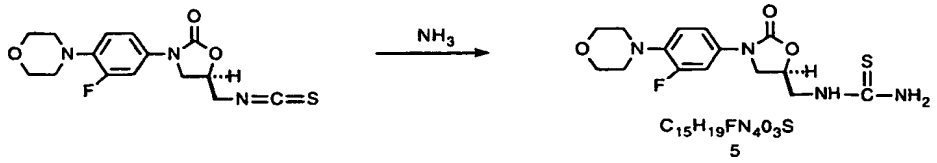
337.0888.

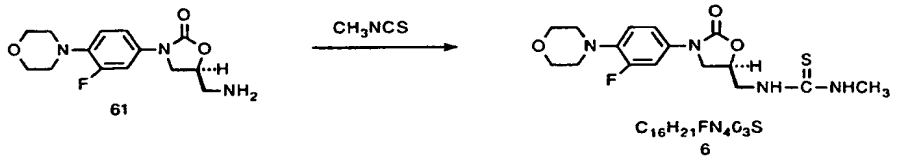
STEP B:



$C_{15}H_{19}FN_4O_3S$
5

Anhydrous ammonia was bubbled for 7 min through a stirred solution of the product from Step I (1.00 g, 2.96 mmol) in THF (10 mL) and the mixture was kept at ambient temperature for 3 h 25 min and concentrated in vacuo. Crystallization of the residue from acetone-hexane gave 0.861 g of 5: mp 199-199.5 °C; MS *m/z* 354 (M^+). Anal. calcd for $C_{15}H_{19}FN_4O_3S$: C, 50.84; H, 5.40; N, 15.81. Found: C, 50.87; H, 5.39; N, 15.72.

EXAMPLE 6: (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-N′-methylthiourea (6).



61

$C_{16}H_{21}FN_4O_3S$
6

A stirred solution of methyl isothiocyanate (93 mg, 1.27 mmol) in THF, was treated with 61 (295 mg, 1.00 mmol), kept at ambient temperature for 18 h and concentrated in vacuo. The residue was recrystallized from EtOAc-hexane to give 246 mg of 6: mp 158-160 °C; MS *m/z* 368 (M^+). Anal. calcd for $C_{16}H_{21}FN_4O_3S$: C, 52.16; H, 5.74; N, 15.21. Found: C, 52.20; H, 5.85; N, 15.17.

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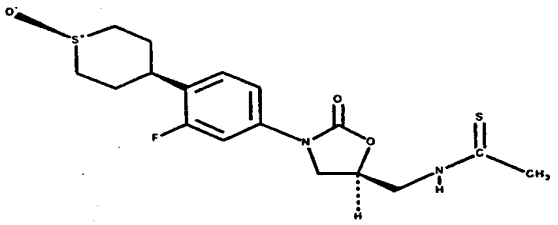
EXAMPLE 7 (S)-cis-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]ethanethioamide



Step 1: A mixture of (S)-(-)-N-[[3-[3-fluoro-4-(3,6-dihydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S-oxide (4.50 g, can be obtained according to the procedures disclosed in International Publication No. WO 97/09328) and platinum oxide (697 mg) in methanol (164 mL) is shaken on the Parr apparatus under a hydrogen atmosphere at 40 psi for 18 hours. The catalyst is then removed by filtration through Celite, and the filtrate is concentrated under reduced pressure and the residue chromatographed on silica gel (230 - 400 mesh, 350 g), eluting with a gradient of methanol/methylene chloride (3/97 - 7/93). Pooling and concentration of those fractions with an R_f = 0.44 by TLC (methanol/chloroform, 10/90) gives (S)-cis-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, mp 203 - 204°C.

Step 2: A mixture of the compound prepared in Step 1 (2.50 g) and hydroxylamine hydrochloride (2.36 g) in pyridine (30.6 mL) and ethanol (3.4 mL) is stirred in a screw-cap vial at 100°C for 22 hrs and at ambient temperature for 16 hrs, during which additional hydroxylamine hydrochloride (944 mg) and pyridine (4 mL) is added. The reaction mixture is then concentrated under reduced pressure, diluted with saturated aqueous sodium bicarbonate (100 mL) and saline (50 mL), adjusted to pH 11 with solid sodium carbonate and extracted with methanol/methylene chloride (10/90, 5 x 100 mL). The combined organic phase is concentrated under reduced pressure, and the crude product is chromatographed on silica gel (230 - 400 mesh, 150 g), eluting with a gradient of methanol/methylene chloride (6/94 - 10/90). Pooling and concentration of those fractions with an R_f = 0.14 by TLC (methanol/chloroform, 10/90) gives (S)-cis-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, mp 159 - 161°C.

Step 3: A solution of ethyl dithioacetate (105 mL, 0.919 mmol) and sodium fluoride (39 mg, 0.919 mmol) in ethanol (9.2 mL) under a nitrogen atmosphere was treated with a mixture of (S)-cis-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-

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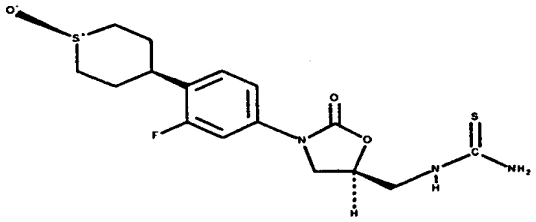
yl)phenyl]-5-aminomethyl-2-oxazolidinone, as prepared in Step 2,(300 mg, 0.919 mmol) and aqueous potassium hydroxide (1M, 0.92 mL) in ethanol (46 mL). The resulting solution was stirred at ambient temperature for 4 hours and was then diluted with methylene chloride (150 mL) and washed with water (50 mL), aqueous potassium hydrogen sulfate (1M, 50 mL) and brine (25 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo*, and the crude product was triturated with methylene chloride/diethyl ether and filtered to give the title compound, mp 176 - 177°C (dec.).

EXAMPLE 8 (S)-cis-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea



Step 1: A solution of 1,1'-thiocarbonyldi-2(1H)-pyridone (235 mg, 1.01 mmol) in anhydrous methylene chloride (10 mL) at 0°C under a nitrogen atmosphere was treated with a solution of (S)-cis-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, as prepared in Example 7, Step 2, (275 mg, 0.843 mmol) in anhydrous methylene chloride (34 mL) over 30 minutes. The resulting mixture was stirred at 0°C for 30 minutes and at ambient temperature for 1 hour and was then diluted with methylene chloride (40 mL), washed with water (25 mL) and brine (25 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was chromatographed on silica gel (70 - 230 mesh, 20 g), eluting with acetonitrile/methylene chloride (40/60), and those fractions with an R_f = 0.07 by TLC (acetonitrile/methylene chloride, 30/70) were pooled and concentrated to give (S)-cis-3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-isothiocyanatomethyl-2-oxazolidinone, mp 187 - 190°C (dec.).

Step 2: A solution of (S)-cis-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-isothiocyanatomethyl-2-oxazolidinone (Step 1, 290 mg, 0.787 mmol) in anhydrous tetrahydrofuran (39 mL) at 0°C under a nitrogen atmosphere was treated

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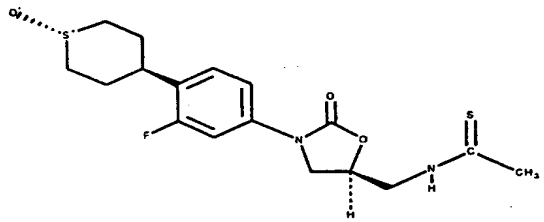
(bubbled) with a stream of ammonia gas for 5 minutes. The reaction pot was sealed, and the resulting mixture was stirred at 0°C for 1 hour. The excess ammonia was then removed under a stream of nitrogen, and the reaction mixture was concentrated *in vacuo* to give the crude product. Recrystallization from methanol/methylene chloride/diethyl ether gave the title compound, mp 206 - 208°C (dec.).

EXAMPLE 9 (S)-trans-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]ethanethioamide



Step 1: (S)-(-)-N-[[3-[3-fluoro-4-(3,6-dihydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-ox azolidinyl]methyl]acetamide S-oxide (disclosed in International Publication No. WO 97/09328) may be reduced to the corresponding cis- and trans-sulfoxides by catalytic hydrogenation in the presence of a catalyst and solvent. Alternatively, the sulfide by product of this reduction reaction can be oxidized with an oxidizing agent such $NaIO_4$ or meta-chloroperoxybenzoic acid in solvent to provide the cis- and trans-sulfoxides. The isomeric mixture can then be separated by chromatography to isolate the trans-sulfoxide, mp 211 - 212°C (dec.). A mixture of the trans-sulfoxide, (S)-trans-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, (0.90 g) and hydroxylamine hydrochloride (0.85 g) in pyridine (11.0 mL) and ethanol (1.2 mL) is stirred in a screw-cap vial at 100°C for 23 hrs and at ambient temperature for 19 hrs, during which additional hydroxylamine hydrochloride (340 mg) and pyridine (1 mL) is added. The reaction mixture is then concentrated under reduced pressure, diluted with saturated aqueous sodium carbonate (50 mL) and saline (50 mL) and extracted with methanol/methylene chloride (10/90, 6 x 100 mL). The combined organic phase is concentrated under reduced pressure, and the crude product is chromatographed on silica gel (230 - 400 mesh, 45 g), eluting with a gradient of methanol/methylene chloride (7.5/92.5 - 10/90). Pooling and concentration of those fractions with an R_f =

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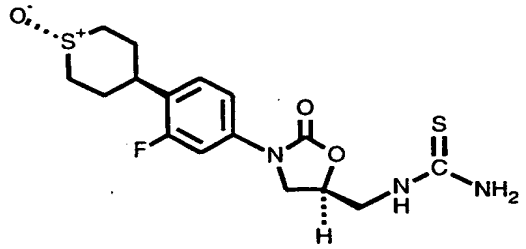
0.14 by TLC (methanol/chloroform, 10/90) gives (S)-trans-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, mp 138 - 140°C.

Step 2: A solution of ethyl dithioacetate (105 mL, 0.919 mmol) and sodium fluoride (39 mg, 0.919 mmol) in ethanol (9.2 mL) under a nitrogen atmosphere was treated with a mixture of (S)-trans-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, as prepare in Step 1, (300 mg, 0.919 mmol) and aqueous potassium hydroxide (1M, 0.92 mL) in ethanol (46 mL). The resulting solution was stirred at ambient temperature for 17 hours and was then diluted with methylene chloride (150 mL), washed with water (2 x 50 mL) and brine (25 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was chromatographed on silica gel (230 - 400 mesh, 35 g), eluting with methanol/methylene chloride (3/97), and those fractions with an R_f = 0.56 by TLC (methanol/chloroform, 10/90) were pooled and concentrated and the residue recrystallized from methylene chloride/diethyl ether to give the title compound, mp 193 - 194°C (dec.).

EXAMPLE 10 (S)-trans-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea



Step 1: A solution of 1,1'-thiocarbonyldi-2(1H)-pyridone (192 mg, 0.827 mmol) in anhydrous methylene chloride (8.3 mL) at 0°C under a nitrogen atmosphere was treated with a solution of (S)-trans-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, as prepared in Example 9, Step 1, (225 mg, 0.689 mmol) in anhydrous methylene chloride (28 mL) over 30 minutes. The resulting mixture was stirred at 0°C for 30 minutes and at ambient temperature for 40 minutes and was then diluted with methylene chloride (20 mL), washed with water (15 mL) and brine (15 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was chromatographed on silica gel (32 - 63 mm, 40 g), eluting with a gradient of acetonitrile/methylene chloride (30/70 -

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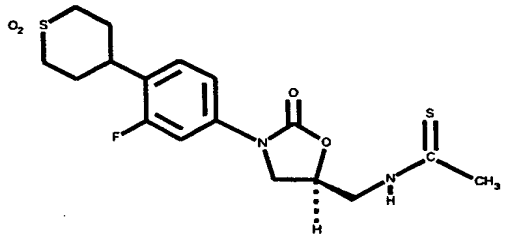
60/40) under 15 psi N_2, and those fractions with an R_f = 0.12 by TLC (acetonitrile/methylene chloride, 30/70) were pooled and concentrated to give (S)-trans-3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4- yl)phenyl]-5-isothiocyanatomethyl-2-oxazolidinone, mp 165 - 167°C.

Step 2: A solution of (S)-trans-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-isothiocyanatomethyl-2-oxazolidinone (Step 1, 230 mg, 0.624 mmol) in anhydrous tetrahydrofuran (31.2 mL) at 0°C under a nitrogen atmosphere was treated (bubbled) with a stream of ammonia gas for 5 minutes. The reaction pot was sealed, and the resulting mixture was stirred at 0°C for 1 hour. The excess ammonia was then removed under a stream of nitrogen, and the reaction mixture was concentrated *in vacuo* to give the crude product. Trituration with methanol/methylene chloride/diethyl ether gave the title compound, mp 209 - 210°C (dec.).

EXAMPLE 11 (S)-N-[[3-[3-Fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]ethanethioamide



Step 1: Starting with (S)-cis-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as prepared in Example 7, Step 1, and following the general procedure of Step 2, and making non-critical variations by substituting (S)-(-)-N-[[3-[3-fluoro-4-(tetrahydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S,S-dioxide (disclosed in International Publication No. WO 97/09328) for (S)-cis-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, the product (S)-(-)-3-[3-Fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone is obtained, mp 194°C (dec.).

Step 2: A solution of ethyl dithioacetate (100 mL, 0.876 mmol) and sodium fluoride (37 mg, 0.876 mmol) in ethanol (8.8 mL) under a nitrogen atmosphere was

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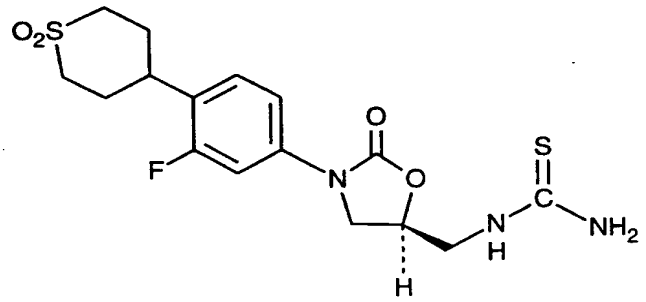
treated with a mixture of (S)-(-)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, as prepared in Step 1, (300 mg, 0.876 mmol) and aqueous potassium hydroxide (1M, 0.88 mL) in ethanol (43.8 mL). The resulting mixture was stirred at ambient temperature for 26 hours, during which additional ethyl dithioacetate (50 mL, 0.438 mmol), sodium fluoride (19 mg, 0.438 mmol), aqueous potassium hydroxide (1M, 0.44 mL) and ethanol (3.0 mL) was added, and was then diluted with methylene chloride (150 mL), washed with water (50 mL), aqueous potassium hydrogen sulfate (1M, 50 mL) and brine (25 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was recrystallized from methylene chloride/diethyl ether to give the title compound, mp 186 - 187°C (dec.).

EXAMPLE 12 (S)-N-[[3-[3-Fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea



Step 1: A solution of 1,1'-thiocarbonyldi-2(1H)-pyridone (304 mg, 1.31 mmol) in anhydrous methylene chloride (13 mL) at 0°C under a nitrogen atmosphere was treated with a solution of (S)-(-)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, as prepared in Example 11, Step 1, (375 mg, 1.09 mmol) in anhydrous methylene chloride (88 mL) over 30 minutes. The resulting mixture was stirred at 0°C for 30 minutes and at ambient temperature for 30 minutes and was then diluted with methylene chloride (40 mL), washed with water (25 mL) and brine (25 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was chromatographed on silica gel (230 - 400 mesh, 45 g), eluting with acetonitrile/methylene chloride (7.5/92.5), and those fractions with an R_f = 0.64 by TLC (acetonitrile/methylene chloride, 20/80) were pooled and concentrated to give (S)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-5-isothiocyanatomethyl-2-oxazolidinone, mp 158 - 162°C (dec.).

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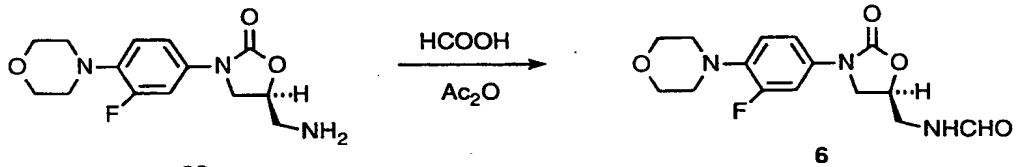
Step 2: A solution of (S)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-5-isothiocyanatomethyl-2-oxazolidinone (Step 1, 380 mg, 0.988 mmol) in anhydrous tetrahydrofuran (49 mL) at 0°C under a nitrogen atmosphere was treated (bubbled) with a stream of ammonia gas for 5 minutes. The reaction pot was sealed, and the resulting mixture was stirred at 0°C for 1 hour. The excess ammonia was then removed under a stream of nitrogen, and the reaction mixture was concentrated *in vacuo* to give the crude product. Recrystallization from methanol/methylene chloride/diethyl ether gave the title compound, mp 196 - 198°C (dec.).

EXAMPLE 13: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-thioformamide (7).**

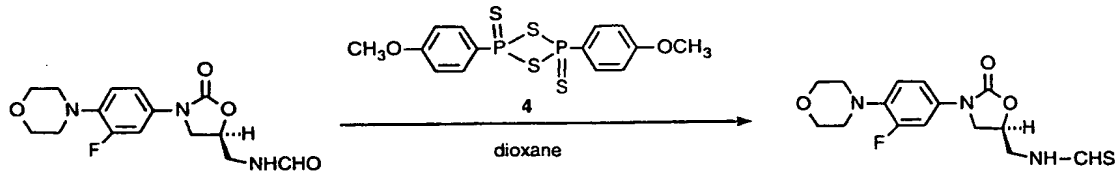
1.



39 6

A stirred mixture of acetic anhydride (0.23 mL, 0.0024 mol) and 95-97% formic acid (0.10 mL, 0.0027 mL) was warmed, under nitrogen at 50-55 °C for 2 h, cooled to ambient temperature and treated, portionwise during 2 min, with **39**[8] (0.45 g, 0.0015 mol). The suspension was kept at ambient temperature for 4 h and the resulting solution was treated with Et_2O (1 mL) and kept at ambient temperature for 18 h. The mixture was diluted with additional Et_2O (10 mL) and the solid was collected by filtration, washed with Et_2O and dried to give 0.38 g of **6**[9]: MS (ES) *m/z* 324 ($M+H^+$), 346 ($M+Na^+$); ^1H NMR (300 mHz, $CDCl_3$) d 3.08 (m, 4H), 3.72 (m, 2H), 3.77 (d,d, 1H), 3.89 (m, 4H), 4.04 (t, 1H), 4.80 (m, 1H), 6.33 (s, 1H), 7.05 (m, 2H), 7.45 (d,d, 1H), 8.27 (s, 1H).

2.



6 7

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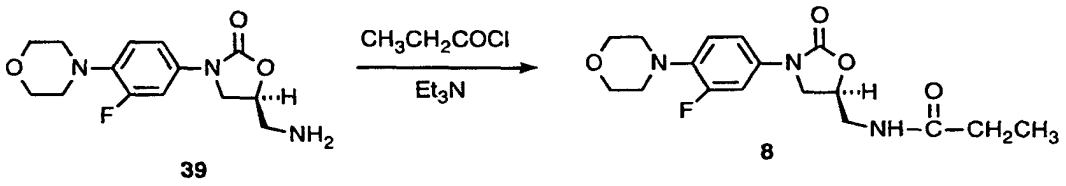
A stirred mixture of **6** (0.38 g, 0.00118 mol) in dioxane (20 mL), under nitrogen was treated with 4 (0.51 g, 0.00126 mol), warmed to reflux during 30 min and kept at this temperature for 90 min. It was then evaporated under a stream of nitrogen. The residue was chromatographed on silica gel with 1.25% MeOH-CH_2Cl_2 and the slightly impure product was rechromatographed on silica gel with 25% EtOAc-CH_2Cl_2. The resulting product was crystallized from EtOAc-methyl *tert*-butyl ether to give 0.114 g of **7**: mp 150-155 °C (dec); IR (DRIFT) 3322, 1752 cm^{-1}; MS(ES) *m/z* 340 ($M+H^+$), 362 ($M+Na^+$); ^{1}HNMR [300 MHz, $(CD_3)_2SO$] d 2.94 (m, 4H), 3.72 (m, 4H), 3.77 (d,d, 1H), 3.94 (t, 2H), 4.12 (t, 1H), 4.93 (m, 1H), 7.05 (t, 1H), 7.16 (d,d, 1H), 7.47 (d,d, 1H), 9.33 (d, 1H), 10.59 (s, 1H). Anal. calcd for $C_{15}H_{18}FN_3O_3S$: C, 53.08; H, 5.35; N, 12.38. Found: C, 53.02; H, 5.44; N, 12.36.

EXAMPLE 14: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiopropion-amide (9).**

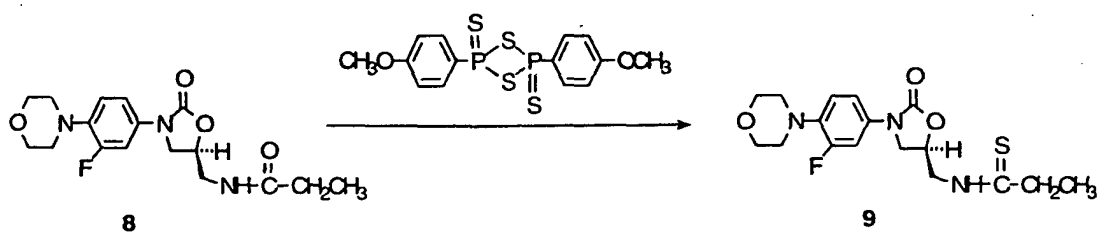
1.



39 8

An ice cold, stirred solution of **39**[8] (0.395 g, 0.00134 mol) and triethyl amine (0.186 mL, 0.0027 mol) in CH_2Cl_2 (20 mL), under nitrogen was treated, dropwise during 2 min, with a solution of propionyl chloride (0.128 mL, 0.00147 mol) in CH_2Cl_2 (3 mL). The mixture was kept in the ice bath for 20 min and at ambient temperature for 1 h. It was then diluted with CH_2Cl_2, washed with saturated $NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated. The residue (**8**)[9] was used without further purification in the next reaction.

2.



8 9

A stirred mixture of the product (**8**) from the previous reaction and dioxane (20 mL), under nitrogen, was treated, portionwise during 1 min, with Lawesson's reagent

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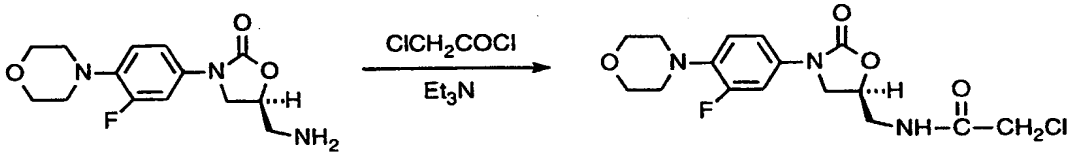
(0.58 g, 0.0014 mol) and refluxed for 2 h; it was then concentrated. The residue was chromatographed on silica gel with 2% MeOH-$CHCl_3$ and the product was crystallized from methyl *tert*-butyl ether to give 0.259 g of **9**: mp 138-139 °C; MS(ES) *m/z* 368 ($M+H^+$), 390 ($M+Na^+$); IR (DRIFT) 3284, 3266, 1748, 1744 cm^{-1}; $[\alpha]^{24}_D$ +20° (MeOH); 1H NMR[300 MHz, $(CD_3)_2SO$] d 1.12 (t, 3H), 2.56 (q, 2H), 2.94 (m, 4H), 3.72 (m, 4H), 3.78 (d,d, 1H), 3.90 (t, 2H), 4.11 (t, 1H), 4.93 (m, 1H), 7.05 (t, 1H), 7.16 (d,d, 1H), 7.47 (d,d, 1H), 10.30 (broad s, 1H). Anal. calcd for $C_{17}H_{22}FN_3O_3S$: C, 55.57; H, 6.03; N, 11.44. Found: C, 55.68; H, 6.21; N, 11.37.

EXAMPLE 15: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-2-chlorothioacetamide (11).**

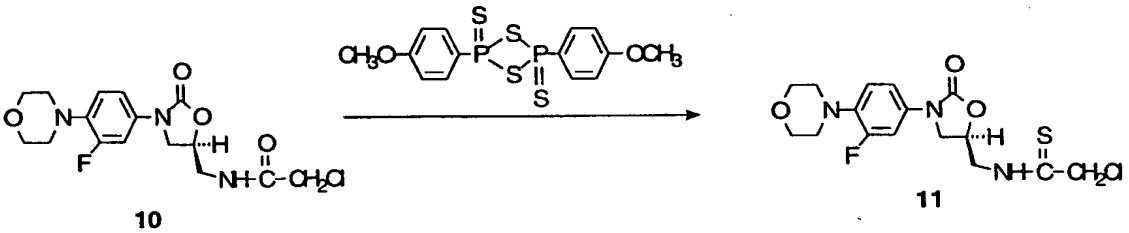
1.



39 10

A stirred solution of **39** (1.54 g, 5.2 mmol) and triethylamine (750 mg, 7.5 mmol) in CH_2Cl_2 (50 mL), under nitrogen, was treated, dropwise, during 15 min with a solution of chloroacetyl chloride (465 mL, 5.8 mmol) in CH_2Cl_2 (30 mL) and kept at ambient temperature for 18 h. It was then washed with saturated $NaHCO_3$ and dilute NaCl, dried (Na_2SO_4) and concentrated. The residue was flash chromatographed on silica gel with 20-30% acetone-CH_2Cl_2 to give 1.49 g of **10**[9] which was used in the next reaction without further purification.

2.



10 11

A stirred mixture of **10** (0.371 g, 1.0 mmol) and Lawesson's reagent (0.420 mg, 1.04 mmol) in dioxane (10 mL) was refluxed, under nitrogen for 2 h and concentrated under reduced pressure. The residue was chromatographed on silica gel with 3-10% acetone-CH_2Cl_2 to give 0.143 g of **11**: MS (CI) *m/z* 388 ($M+H^+$); ^1H NMR (300 MHz, $CDCl_3$) d 3.07 (m, 4H), 3.77 (d,d, 1H), 3.88 (m, 4H), 4.04 (m, 1H), 4.12 (t, 1H),

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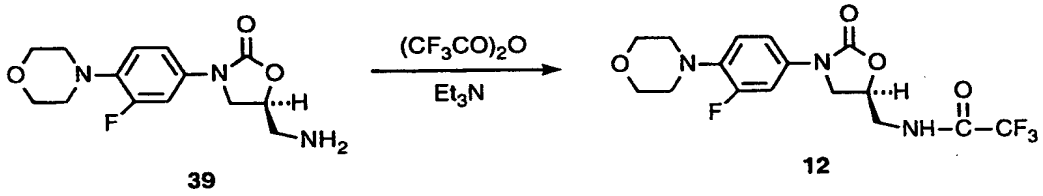
4.35 (m, 1H), 4.61 (s, 2H), 4.98 (m, 1H), 6.96 (t, 1H), 7.08 (d,d, 1H), 7.44 (d,d, 1H), 8.69 (s, 1H). Anal. calcd for $C_{16}H_{19}ClFN_3O_3S$: C, 49.55; H, 4.94; N, 10.83. Found: C, 49.38; H, 5.20; N, 10.27.

EXAMPLE 16: **(*S*)-N-[[3-[3-Fluoro-4-(4-moropholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α,α,α-trifluorothioacetamide (13).**

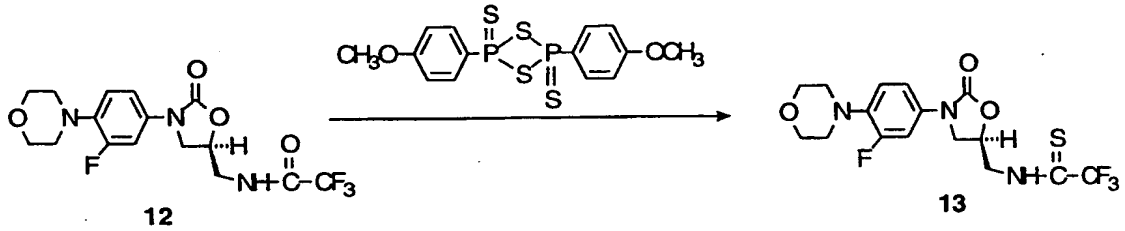
1.



39 12

An ice cold stirred solution of **39** (0.590 g, 2.0 mmol) and triethylamine (640 mL, 4.6 mmol) in CH_2Cl_2 (10 mL) was treated with trifluoroacetic anhydride (325 mL, 2.3 mmol) and kept in the ice bath for 10 min and then at ambient temperature. The reaction was followed by TLC on silica gel with 30% acetone-CH_2Cl_2. Additional trifluoroacetic anhydride and triethylamine were added after 3 d (64 mL / 125 mL), 4 d (100 mL / 220 mL) and 6 d (325 mL / 1.0 mL). The reaction was complete 1 h after the last addition; it was mixed with CH_2Cl_2, washed with water and dilute NaCl, dried (Na_2SO_4) and concentrated. The solid residue was recrystallized from acetone-heptane to give 0.566 g of **12**: mp 161-164 °C (dec); MS(EI) *m/z* 391 (M^+). Anal. calcd for $C_{16}H_{17}F_4N_3O_4$: C, 49.11; H, 4.38; N, 10.74. Found: C, 48.99; H, 4.56; N, 10.73.

2.



12 13

A stirred mixture of **12** (0.391 g, 1.0 mmol) and Lawesson's reagent (0.422 g, 1.1 mmol) in dioxane (10 mL) was refluxed, under nitrogen for 2 h, cooled slowly to ambient temperature and concentrated in vacuo. The residue was flash chromatographed on silica gel with 5-15% acetone-CH_2Cl_2 and the product was crystallized from acetone-heptane to give 0.249 g of **13**: mp 151-152 °C; MS(EI) *m/z* 407 (M^+), 363, 209, 151, 95; ^1H NMR (300 MHz, $CDCl_3$) d 3.05 (m, 4H), 3.75 (d,d,

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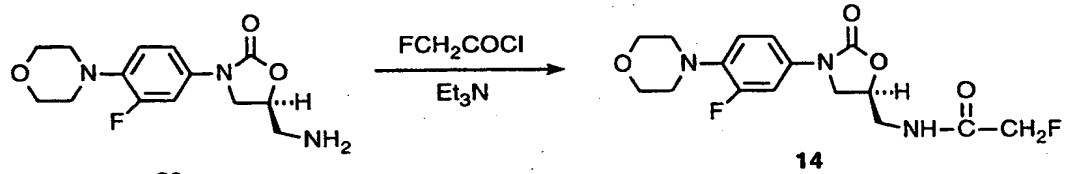
1H), 3.87 (m, 4H), 3.95 (m, 1H), 4.14 (t, 1H), 4.32 (m, 1H), 5.01 (m, 1H), 6.92 (t, 1H), 7.05 (d,d, 1H), 7.38 (d,d, 1H), 9.03 (s, 1H). Anal. calcd for $C_{16}H_{17}F_4N_3O_3S$: C, 47.17; H, 4.21; N, 10.31. Found: C, 47.09; H, 4.35; N, 10.27.

EXAMPLE 17: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α-fluorothioacetamide (15).**

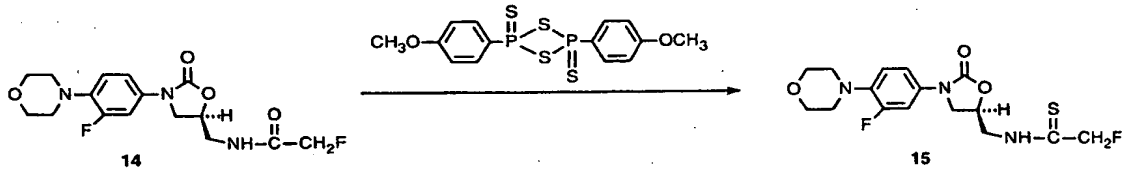
1.



39 14

A stirred, ice cold solution of **39** (0.590 g, 2.0 mmol) and triethylamine (611 mL, 4.4 mmol) in CH_2Cl_2 (10 mL), under nitrogen, was treated, dropwise, with a solution of fluoroacetyl chloride (220 mL, 2.2 mmol) in CH_2Cl_2 (5 mL), kept in the ice bath for 10 min and at ambient temperature for 2 h. It was then diluted with CH_2Cl_2, washed with water and dilute NaCl, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with 10-30% acetone-CH_2Cl_2 to give 0.180 g of **14**: MS(ES) *m/z* 356 ($M+H^+$), 378 ($M+Na^+$).

2.



14 15

A solution of **14** (0.180 g, 0.507 mmol) in dioxane, under nitrogen, was treated with Lawesson's reagent (0.206 g, 0.51 mmol), warmed at 90-100 °C for 1 h and concentrated in vacuo. The residue was chromatographed on silica gel with 15% acetone-CH_2Cl_2 to give 0.161 g of **15**: MS(EI) *m/z* 371 (M^+); ^1H NMR (300 MHz, $CDCl_3$) d 3.05 (m, 4H), 3.78 (d,d, 1H), 3.87 (m, 4H), 4.03 (m, 1H), 4.11 (t, 1H), 4.38 (m, 1H), 4.98 (m, 1H), 5.07 (s, 1H), 5.23 (s, 1H), 6.93 (t, 1H), 7.08 (dd, 1H), 7.42 (d,d, 1H), 8.42 (s, 1H). Anal. calcd for $C_{16}H_{19}F_2N_3O_3S$: C, 51.74; H, 5.16; N, 11.31. Found: C, 51.79; H, 5.31; N, 11.02.

EXAMPLE 18: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α,α-difluorothioacetamide (17).**

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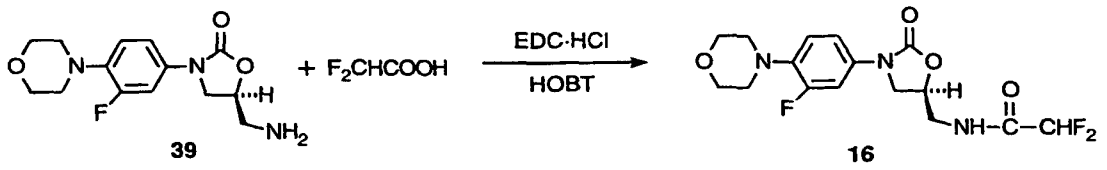
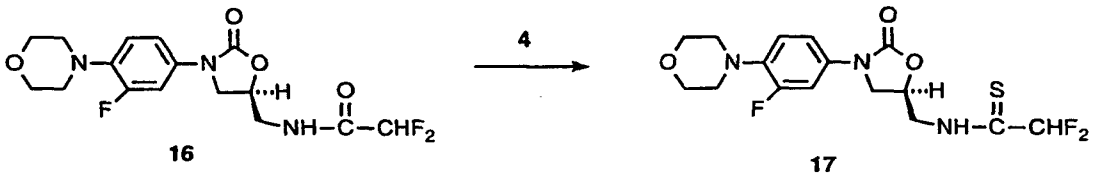
1.



A stirred, ice cold mixture of **39** (0.590 g, 2.0 mmol), difluroacetic acid (190 mL, 2.0 mmol), and 1-hydroxybenzotriazole (0.297 g, 2.2 mmol) in DMF (5 mL) under nitrogen, was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.843 g, 4.4 mmol) and kept at ambient temperature for 18 h. It was diluted with CH_2Cl_2, washed with water and dilute NaCl, dried (Na_2SO_4) and concentrated. The solid residue was crystallized form EtOAc-heptane to give 0.617 g of **16**: mp 149-150 °C; 1H NMR (300 MHz, CDCl3) d 3.05 (m, 4H), 3.66 (m, 2H), 3.85 (m, 5H), 4.08 (t, 1H), 4.80 (m, 1H), 5.93 (t, J = 53.9 Hz, 1H), 6.92 (t, 1H), 7.06 (m, 2H), 7.39 (d,d, 1H); MS(EI) m/z 373 (M^+). Anal. calcd for $C_{16}H_{18}F_3N_3O_4$: C, 51.48; H, 4.86; N, 11.26. Found: C, 51.59; H, 4.91; N, 11.29.

2.



A stirred solution of **16** (0.373 g, 1.00 mmol) in dioxane (10 mL), under nitrogen was treated with Lawesson's reagent (0.404 g, 1.00 mmol), warmed at about 95 °C for 1 h and concentrated in vacuo. Chromatography of the residue on silica gel with 10% acetone-CH_2Cl_2 and cyrstallization of the product from EtOAc-heptane gave 0.276 g of **17**: mp 125-127 °C; MS(EI) m/z 389 (M^+), 345, 305, 247, 209, 195, 151, 138, 123, 109, 95; ^1H NMR (300 MHz, $CDCl_3$) d 3.05 (m, 4H), 3.76 (d,d, 1H), 3.86 (m, 4H), 4.01 (m, 1H), 4.12 (t, 1H), 4.30 (m, 1H), 4.99 (m, 1H), 6.20 (t, J = 55.9 Hz, 1H), 6.92 (t, 1H), 7.06 (d,d, 1H), 7.38 (d,d, 1H), 8.78 (broad s, 1H). Anal. calcd for $C_{16}H_{18}F_3N_3O_3S$: C, 49.35; H, 4.66; N, 10.79. Found: C, 49.37; H, 4.71; N, 10.83.

EXAMPLE 19: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α-cyanothioacetamide (19).**

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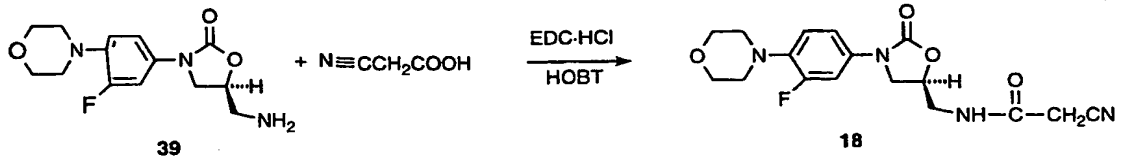
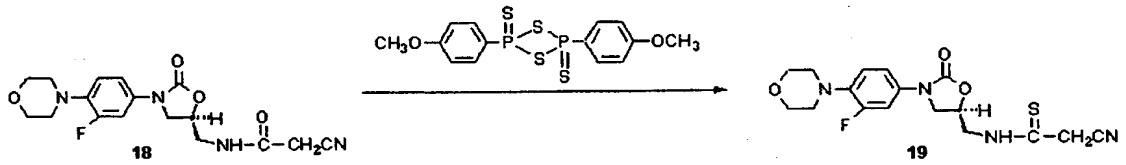
1.



39 18

An ice cold, stirred mixture of **39** (0.646 g, 2.19 mmol), cyanoacetic acid (0.179 g, 2.1 mmol) and 1-hydroxybenzotriazole (0.351 g, 2.6 mmol) in DMF (5 mL), under nitrogen, was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.997 g, 5.2 mmol) and kept at ambient temperature for 24 h. It was diluted with CH_2Cl_2, washed with water and dilute NaCl, dried (Na_2SO_4) and concentrated. The solid residue was crystallized from EtOAc-heptane to give 0.546 g of **18**: mp 172-174 °C: IR (DRIFT) 3316, 2256, 1754, 1684 cm^{-1}; MS(EI) *m/z* 362 (M^+). Anal. calcd for $C_{17}H_{19}FN_4O_4$: C, 56.35; H, 5.28; N, 15.46. Found: C, 56.33; H, 5.30; N, 15.36.

2.



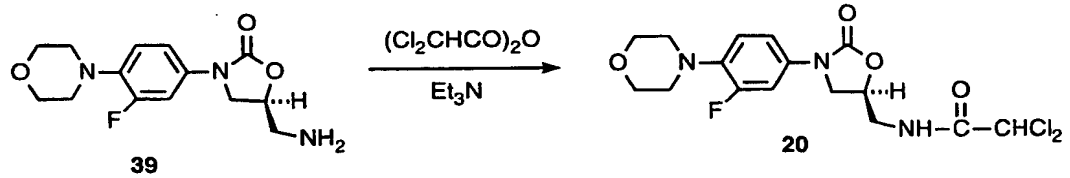
18 19

A stirred solution of **18** (0.453 mg, 1.25 mmol) in dioxane (10 mL), under nitrogen, was treated with Lawesson's reagent (0.505 g, 1.25 mmol) and warmed at about 100 °C. When the reaction was over (TLC with 30% acetone-CH_2Cl_2) the mixture was cooled and concentrated in vacuo. Chromatography of the residue on silica gel with 10-20% acetone-CH_2Cl_2 and crystallization of the product from EtOAc-heptane gave 0.110 g of **19**: mp 186-187 °C (dec); MS(ES) *m/z* 379 ($M+H^+$), 401 ($M+Na^+$); ^1H NMR (300 MHz, $CDCl_3$) d 3.05 (m, 4H), 3.81 (d,d, 1H), 3.86 (m, 4H), 3.89 (s, 2H), 4.09 (t, 1H), 4.14 (m, 2H), 5.01 (m, 1H), 6.92 (t, 1H), 7.05 (d,d, 1H), 7.34 (d,d, 1H), 9.15 (s, 1H); IR (DRIFT) 3244, 2260, 1754 cm^{-1}. Anal. calcd for $C_{17}H_{19}FN_4O_3S$: C, 53.96; H, 5.06; N, 14.81. Found: C, 53.88; H, 5.39; N, 14.61.

EXAMPLE 20: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α,α-dichlorothioacetamide (21).**

BNSDOCID: <WO 9854161A1 IA>

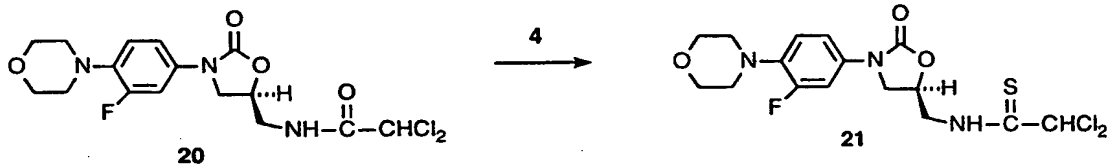
1.



39 20

A stirred, ice cold solution of **39** (0.885 g, 3.00 mmol) and triethylamine (975 mL, 7 mmol) in CH_2Cl_2 (15 mL), under nitrogen was treated, dropwise with a solution of dichloroacetic anhydride (555 mL, 3.5 mmol) in CH_2Cl_2 (5 mL) and kept in the ice bath for 15 min and at ambient temperature for 18 h. It was diluted with CH_2Cl_2, washed with water, saturated $NaHCO_3$ and dilute NaCl, dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with 10% acetone-CH_2Cl_2 and crystallization of the product from acetone-heptane gave 0.463 g of **20**: mp 197-198 °C (dec); MS(ES) *m/z* 406 ($M+H^+$), 428 ($M+Na^+$); ^1H NMR (300 MHz, $CDCl_3$) d 3.05 (m, 4H), 3.75 (m, 3H), 3.86 (m, 4H), 4.07 (t, 1H), 4.83 (m, 1H), 5.94 (s, 1H), 6.92 (t, 1H), 7.06 (m, 2H), 7.41 (d,d, 1H).

2.

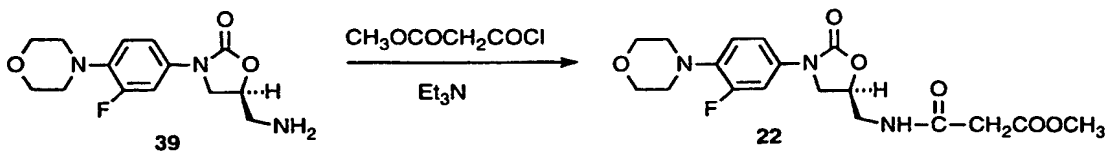


20 21

A stirred solution of **20** (0.305g, 0.75 mmol) in dioxane (5 ml), under nitrogen, was treated with Lawesson's reagent (0.202g, 0.5 mmol), warmed at about 90°C for 1 hour, cooled and concentrated in vacuo. Chromatography of the residue on silica gel first with 30% acetone-heptane and then with 10% acetone-methylene chloride and crystallization of rh product form methylene chloride - heptane gave 0.203g with **21**: mp 143-144°cd.; HR17S (EI) calculated for $C_{16}H_{18}cl_2$ F N_3 O_3 S(M) 421.0431. Anal. calcd for $C_{16}H_{18}cl_2$ F N_3 O_3 S, C, 45.51; H, 4.30; N, 9.95. Found: C, 45.47; H, 4.24; H, 9.88.

EXAMPLE 21: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α-(methoxycarbonyl)thioacetamide (23).**

1.



39 22

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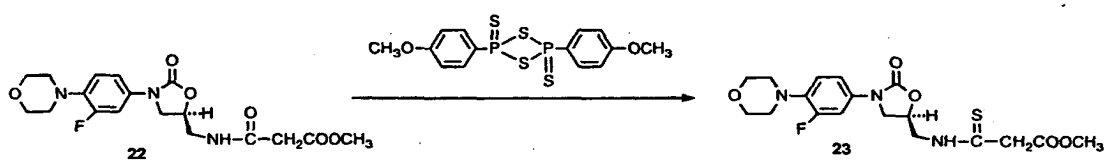
A stirred solution of **39** (0.955 g, 3.2 mmol) and triethylamine (650 mL, 4.5 mmol) in CH_2Cl_2 (50 mL), under nitrogen, was treated, dropwise during 15-20 min with a solution of methyl malonyl chloride (475 mL, 4.3 mmol) in CH_2Cl_2 (10 mL) and kept at ambient temperature for 3 days. It was then washed with water and dilute NaCl, dried and concentrated. The residue was flash chromatographed on silica gel with 15-30% acetone-CH_2Cl_2 and the product was crystallized form acetone-hexane to give 0.873 g of **22**: mp 150-151 °C; ^{1}H NMR (300 MHz, $CDCl_3$) d 3.03 (m, 4H), 3.34 (s, 2H), 3.67 (s, 3H), 3.69 (m, 2H), 3.76 (d,d, 1H), 3.85 (m, 4H), 4.00 (t, 1H), 4.78 (m, 1H), 6.90 (t, 1H), 7.06 (d,d, 1H), 7.41 (d,d, 1H), 7.57 (t, 1H); MS(ES) *m/z* 396 ($M+H^+$), 418 ($M+Na^+$); HRMS (FAB) calcd for $C_{18}H_{23}FN_3O_6$ ($M+H^+$) 396.1571, found 396.1579. Anal. calcd for $C_{18}H_{22}FN_3O_6$: C, 54.68; H, 5.61; N, 10.63. Found: C, 54.69; H, 5.68; N, 10.58.

2.



A stirred solution of **22** (0.395 g, 1.0 mmol) in dioxane (10 mL), under nitrogen, was treated with Lawesson's reagent (0.202 g, 0.5 mmol) and kept at ambient temperature for 4 h 10 min and at 80-90 °C for 1.5 h. The reaction was followed by TLC on silica gel with 10% MeOH-$CHCl_3$. At this time a new, less polar product had begun to form. It was kept at ambient temperature for 18 h and at 80 °C for 2 h; additional Laewsson's reagent (40 mg, 0.099 mmol) was added and warming at 80 °C was continued for 2 h; some starting material still remained. The mixture was concentrated and the residue was chromatographed on silica gel with 15% acetone-CH_2Cl_2 to give 0.348 g of **23**: ^{1}H NMR (300 MHz, $CDCl_3$) d 3.05 (m, 4H), 3.71 (s, 3H), 3.81 (d,d, 1H), 3.86 (m, 4H), 3.88 (s, 2H), 4.07 (t, 1H), 4.19 (m, 2H), 4.99 (m, 1H), 6.91 (t, 1H), 7.07 (d,d, 1H), 7.42 (d,d, 1H), 9.52 (s, 1H); IR (DRIFT) 3269, 1743 cm^{-1}; MS(EI) *m/z* 411 (M^+). Anal. calcd for $C_{18}H_{22}FN_3O_5S$: C, 52.54; H, 5.39; N, 10.21. Found: C, 52.58; H, 5.43; N, 10.14.

EXAMPLE 22: **(*S*)-N-[[3-[4-[1-[1,2,4]Triazolyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (25).**

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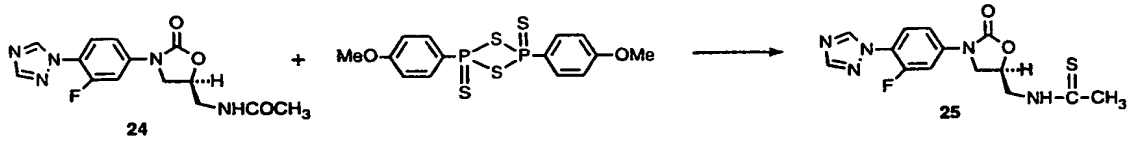
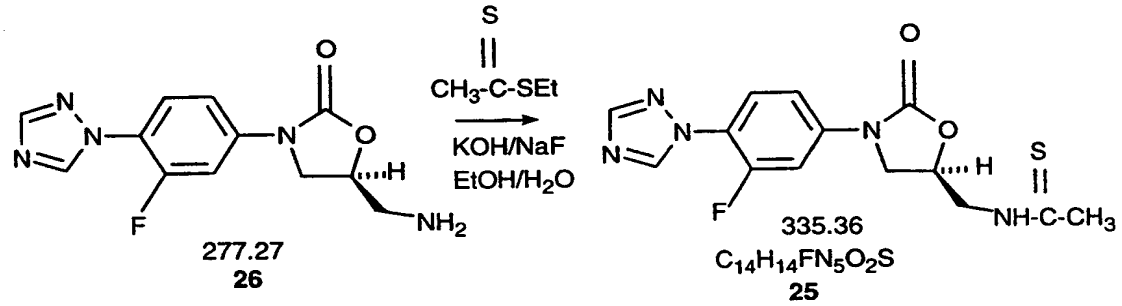


A stirred mixture of **24**[10,11] (0.150 g, 0.470 mmol) and dioxane (12.5 mL), under nitrogen, was treated with Lawesson's reagent (0.20 g, 0.50 mmol), refluxed for 1.5 h, kept at ambient temperature for 18 h and concentrated in vacuo. Flash chromatography of the residue on silica gel with 5% MeOH-$CHCl_3$ gave the product which was crystallized from MeOH to give 0.100 g (63.4%) of **25**: mp 161-163 °C; ^1H NMR [300 MHz, $(CD_3)_2SO$] d 2.43 (s, 3H), 3.87 (m, 3H), 4.22 (t, 1H), 4.99 (m, 1H), 7.51 (d, 1H), 7.77 (m, 2H), 8.26 (s, 1H), 8.97 (d, 1H), 10.35 (broad s, 1H); IR (mull) 3259, 3226, 3044, 1752 cm^{-1}; MS(ES) *m/z* 336 ($M+H^+$), 358 ($M+Na^+$). Anal. calcd for $C_{14}H_{14}FN_5O_2S$: C, 50.14; H, 4.21; N, 20.88. Found: C, 50.18; H, 4.26; N, 20.94.

EXAMPLE 23: **(*S*)-N-[[3-[4-[1-[1,2,4]Triazolyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (25).**



A stirred mixture of **26**[10,12] (0.26 g, 0.938 mmol), ethyl dithioacetate (0.12 g, 0.998 mmol), sodium fluoride (0.040 g, 0.953 mmol) and absolute EtOH (10 mL), under nitrogen, was treated during 5 min with a solution of 0.97 M KOH (1.03 mL) in EtOH and kept at ambient temperature for 2 h. It was then diluted with CH_2CL_2 (75mL), washed with water, 1M $KHSO_4$, water and brine and evaporated. The residue was flash chromatographed on silica gel with 5% MeOH-$CHCl_3$ and the product was crystallized from MeOH to give 0.118 g, mp 164-165°C (dec) and 0.026 g, mp 162-163°C (dec) of **25**.

EXAMPLE 24: **(*S*)-N-[[3-[1-(Hydroxyacetyl)-5-indolinyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (28).**

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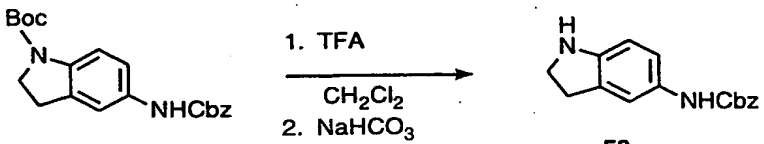
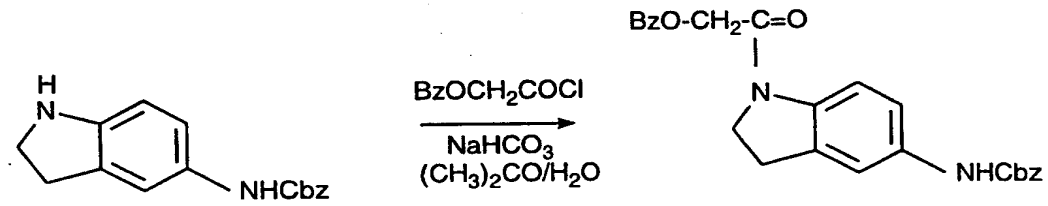
1.



52 53

A stirred, ice cold solution of **52**[13,14] (8.80 g, 0.0240 mol) in CH_2Cl_2 (25 mL) was treated during 20 min with a solution of trifluoroacetic acid (25 mL) in CH_2Cl_2 (10 mL). The mixture was kept in the ice bath for 2 h 15 min and concentrated under reduced pressure. A solution of the residue in CH_2Cl_2 was washed with saturated $NaHCO_3$ and dilute NaCl, dried (Na_2SO_4) and concentrated. The residue was used in the next reaction without further purification. A sample of this material (**53**) had: ^1H NMR (300 MHz, $CDCl_3$) d 3.00 (t, 2H), 3.54 (t, 2H), 3.85 (broad s, 1H), 5.17 (s, 2H), 6.59 (d, 1H), 6.66 (broad s, 1H), 6.91 (d, 1H), 7.23 (s, 1H), 7.36 (m, 5H); MS *m/z* 269 ($M+H^+$).

2.



268.22
$C_{16}H_{16}N_2O_2$
53

416.48
$C_{25}H_{24}N_2O_4$
54

An ice cold, stirred mixture of **53** (crude product from the previous reaction), acetone (200 mL), saturated $NaHCO_3$ (200 mL) and water (30 mL) was treated, dropwise during 20 min, with a solution of benzyloxyacetyl chloride (4.70 mL, 0.030 mol) in acetone (55 mL), warmed slowly to ambient temperature and kept for 18 h. Additional benzyloxytacetyl chloride (1.0 mL) in acetone 35 mL) was added dropwise and the mixture was kept at ambient temperature for an additional 3 h and diluted with EtOAc and water. A solid was collected by filtration and dried to give 4.00 g of crude product. The EtOAc solution was dried (Na_2SO_4) and concentrated to give 5.36 g of additional crude product. Crystallization of the product from EtOAc gave a total of 6.35 g of **54**[14], mp 157-159.5°C. The analytical sample had: mp 158-159.5°C; ^1H NMR (300 MHz, $CDCl_3$) δ 3,16 (t,2H), 4.01(t,2H), 4.21 (s, 2H), 4.69 (s,

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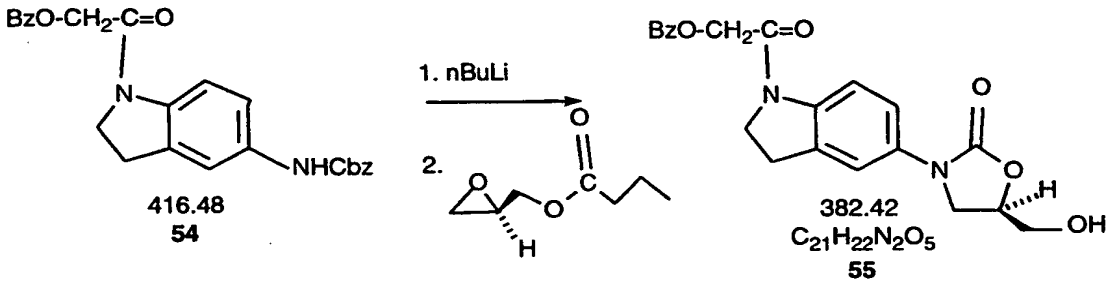
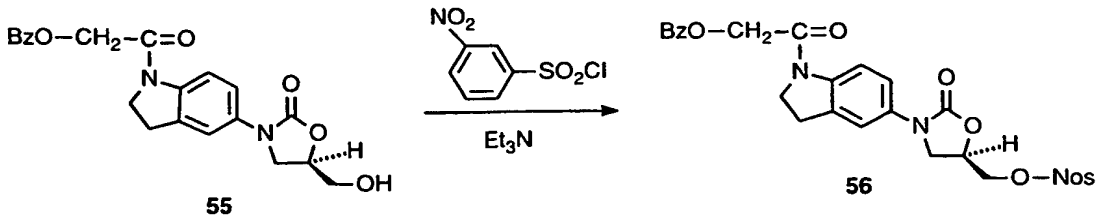
2H), 5.19 (s, 2H), 6.67 (s, 1H), 6.97 (d, 1H), 7.36 (m, 10H), 7.50 (braod s, 1H), 8.15 (d, 1H); MS(EI) *m/z* (relative intensity) 416 (M^+, 9), 310 (8), 202 (10), 133 (8), 92 (8), 91 (99), 79 (7), 77 (9), 65 (12), 51 (6); IR (mull) 2381, 1722, 1659, 1608, 1558 cm^{-1}. Anal. calcd for $C_{25}H_{24}N_2O_4$: C, 72.10; H, 5.81; N, 6.73. Found: C, 72.05; H, 5.86; N, 6.68.

3.



A stirred suspension of **54** (1.16 g, 2.78 mmol) in THF (42 mL) was cooled, under nitrogen, to -78°C and treated, dropwise, during 5 min with 1.6 M n-BuLi in hexane (1.83 mL). It was kept at -78°C for 50 min, treated, dropwise, during 5 min with a solution of (R)-(-)-glycidyl butyrate (0.500 g, 3.47 mmol) in THF (2 mL), allowed to warm to ambient temperature during 3 h and kpet for 18 h. It was then diluted with EtOAc, washed with saturated NH_4Cl, water and brine, dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel with 3% MeOH-0.2% NH_4OH-$CHCl_3$ gave 0.60 g (56%) of **55**[14]: ^1H NMR [300 MHz, $(CD_3)_2SO$] δ 3.14 (t, 2H), 3.59 (m, 2H), 3.79 (d,d, 1H), 4.03 (m, 3H), 4.29 (s, 2H), 4.58 (s, 2H), 4.65 (m, 1H), 5.20 (t, 1H), 7.31 (m, 6H), 7.55 (s, 1H), 8.03 (d, 1H); MS(ES) *m/z* 383 ($M+H^+$), 405 ($M+Na^+$).

4.



An ice cold, stirred mixture of **55** (0.60 g, 1.57 mmol), triethylamine (2.2 mL), and CH_2Cl_2 (12 mL), under nitrogen, was treated with 3-nitrobenzenesulfonyl chloride (0.44 g, 1.99 mmol) and kept in the ice bath for 30 min and at ambient temperature for 60 min. It was then diluted with CH_2Cl_2, washed with water and brine, dried

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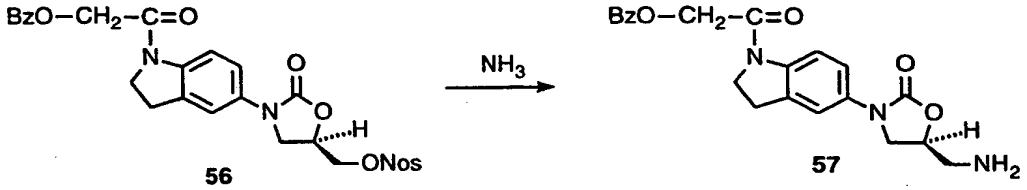
(Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with 15% CH_3CN-CH_2Cl_2 gave 0.70 g of **56**: ^1H NMR (300 MHz, $CDCl_3$) d 3.19 (t, J = 8.3 Hz, 2H), 3.88 (d,d, 1H), 4.04 (t, J = 8.4 Hz, 2H), 4.14 (t, 1H), 4.23 (s, 2H), 4.42 (m, 2H), 4.70 (s, 2H), 4.84 (m, 1H), 6.97 (m, 1H), 7.34 (m, 5H), 7.58 (s, 1H), 7.81 (t, 1H), 8.22 (m, 2H), 8.53 (m, 1H), 8.73 (m, 1H); MS(ES) m/z 568 ($M+H^+$), 590 ($M+Na^+$).

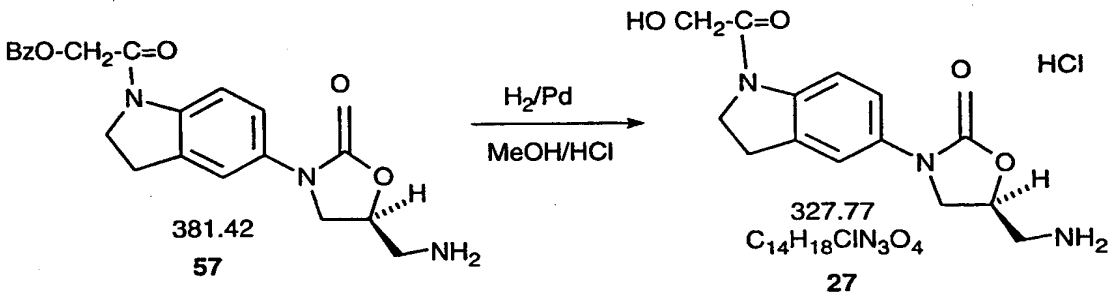
5.



56 57

A stirred mixture of **56** (crude product from 0.00314 mol of **55**), acetonitride (70 mL), isopropanol (70 mL) and 29% ammonium hydroxide (70 mL) was warmed at 40-44 °C for 7h and kept at ambient temperature for 18 h. It was concentrated in vacuo to an aqueous residue with was extracted with CH_2Cl_2. The extract was washed with water and brine, dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with 8% MeOH-0.5% NH_4OH-$CHCl_3$ gave 1.05 g of **57**: ^1H NMR [300 MHz, $(CD_3)_2SO$] d 2.78 (m, 2H), 3.13 (t, 2H), 3.82 (d,d, 1H), 4.01 (m, 3H), 4.29 (s, 2H), 4.58 (s, 2H), 4.58 (m, 1H), 7.31 (m, 6H), 7.54 (broad s, 1H), 8.03 (d, 1H); MS(ES) m/z 382 ($M+H^+$), 404 ($M+Na^+$).

6.



A mixture of **57** (0.46 g, 1.21 mmol), MeOH (150 mL), 1 M HCl (1.2 mL) and 5% palladium-on-carbon catalyst (250 mg) was hydrogenated at an initial pressure of 49 psi for 5 h. Additional 1M HCl (0.5 mL) and catalyst (100 mg) were added and hydrogenation was continued for 18 h. The catalyst was removed by filtration and

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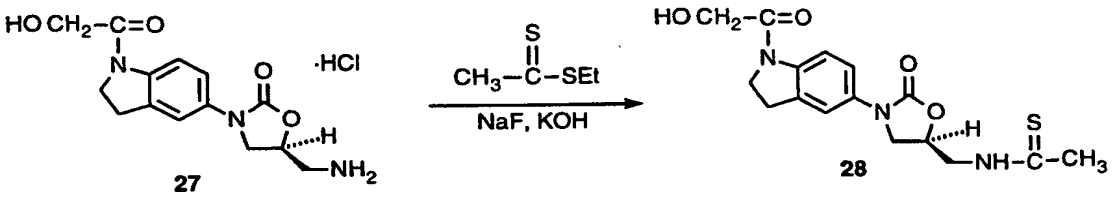
the filtrate was concentrated to give 0.34 g of **27**: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ 3.15 (t, 2H), 3.22 (broad s, 2H), 3.84 (d,d, 1H), 4.00 (t, 2H), 4.15 (s, 2H), 4.15 (m, 1H), 4.92 (m, 1H), 7.24 (q, 1H), 7.50 (d, 1H), 8.03 (d, 1H), 8.37 (broad s, 3H); MS(ES) *m/z* 2.92 ($M+H^+$).

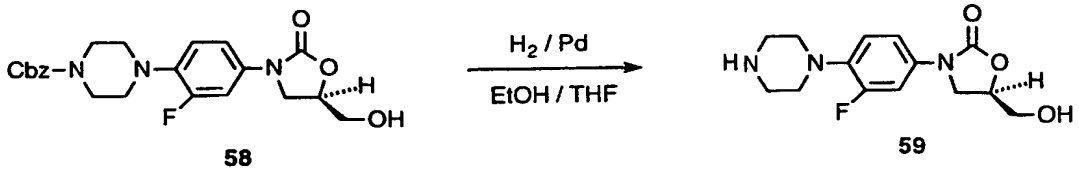
7.



A suspension of **27** (0.10 g, 0.34 mmol) in a mixture of EtOH (15 mL) and 0.97 M KOH (0.7 mL) was added, under nitrogen to a stirred mixture of ethyl dithioacetate (0.0412 g, 0.343 mmol) and sodium fluoride (0.0137 g, 0.326 mmol) in EtOH (5 mL) and the mixture was kept at ambient temperature for 2h 15 min. Additional 0.97 M KOH (0.2 mL), sodium iodide (6 mg) and ethyl dithioacetate (20 mg) were added and the mixture was stirred for 2 h, mixed with CH_2Cl_2 (150 mL), washed with water, 1M $KHSO_4$ and brine, dried (Na_2SO_4) and concentrated. The residue was crystallized from acetone to give 0.0404 g of **28**: mp 175-176 °C (dec); MS (FAB) *m/z* 350 ($M+H^+$), 349 (M^+), 331, 316, 205, 73; HR MS (FAB) calcd for $C_{16}H_{20}N_3O_4S$ ($M+H^+$) 350.1174, found 350.1183; ^{1}H NMR [300 MHz, $(CD_3)_2SO$] d 2.42 (s, 3H), 3.14 (t, 2H), 3.79 (d,d, 1H), 3.89 (t, 2H), 4.00 (t, 2H), 4.12 (m, 3H), 4.83 (t, 1H), 4.90 (m, 1H), 7.25 (d, 1H), 7.50 (s, 1H), 8.03 (d, 1H), 10.35 (s, 1H); IR (DRIFT) 3255, 3223, 3068, 1747, 1639, 1614 cm^{-1}.

EXAMPLE 25: **(*S*)-N-[[3-[3-Fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (30).**

1.



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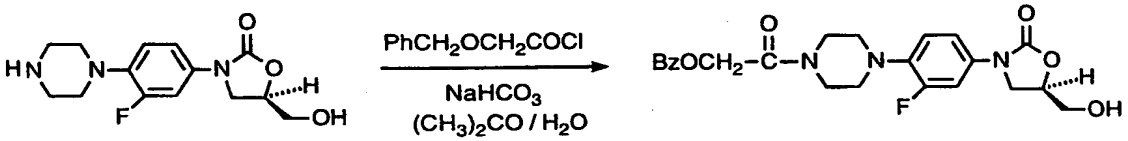
A mixture of **58**[15] (3.00 g, 7.00 mmol), THF (60 mL), absolute EtOH (100 mL) and 10% palladium-on-carbon catalyst (415 mg) was hydrogenated at an initial pressure of 58 psi for 2 h 50 min. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give 2.67 g of **59** which was used without further purification in the next reaction: ^{1}H NMR (300 MHz, $CDCl_3$) d 2.16 (broad s), 3.02 (m, 8H), 3.73 (d,d, J = 3.9, 12.6 Hz, 1H), 3.96 (m, 3H), 4.72 (m, 1H), 6.92 (t, J = 9.2 Hz, 1H), 7.11 (m, 1H), 7.43 (d,d, J = 2.6, 14.3 Hz, 1H); MS(ES) m/z 296 ($M+H^+$).

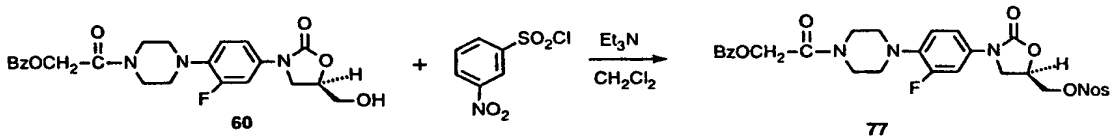
2.



59 **60**

A stirred, ice cold mixture of **59** (2.67 g from the previous reaction), acetone (190 mL) and saturated $NaHCO_3$ (70 mL) was treated, dropwise during 2-3 min with a solution of benzyloxyacetyl chloride (1.34 mL, 8.61 mmol) in acetone (25 mL), kept in the ice bath for 1 h and diluted with EtOAc. The aqueous layer was extracted with EtOAc and the combined organic solution was washed with dilute NaCl, dried and concentrated. Chromatography of the residue on silica gel with 30% acetone-CH_2Cl_2 gave 2.64 g of **60**: ^{1}H NMR (300 MHz, $CDCl_3$) d 2.28 (broad s, 1H), 3.00 (m, 4H), 3.66 (m, 2H), 3.77 (m, 3H), 3.96 (m, 3H), 4.22 (s, 2H), 4.61 (s, 2H), 4.74 (m, 1H), 6.88 (t, J = 9.2 Hz, 1H), 7.12 (m, 1H), 7.35 (s, 5H), 7.46 (d,d, J = 2.6, 14.2 Hz, 1H); IR (mull) 3406, 1748, 1647 cm^{-1}; HRMS(EI) calcd for $C_{23}H_{26}FN_3O_5$ (M^+) 443.1856, found 443.1842.

3.



60 **77**

A stirred, ice cold mixture of **60** (2.64 g, 6.00 mmol) and triethylamine (1.14 mL, 8.16 mmol) in CH_2Cl_2 (200 mL), under nitrogen, was treated with 3-nitrobenzenesulfonyl chloride (1.78 g, 8.04 mmol), warmed to ambient temperature and kept for 5 h 20 min. Additional 3-nitrobenzenesulfonyl chlroide (180 mg) and triethylamine (0.20 mL) were added and the mixture was kept at ambient

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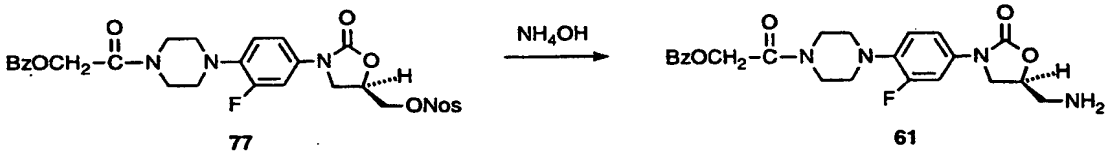
temperature for 18 h, diluted with CH_2Cl_2 and washed with water and dilute NaCl, dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with 40-60% acetone-hexane gave 3.36 g of **77**: ^{1}H NMR (300 MHz, $CDCl_3$) d 3.02 (broad s, 4H), 3.66 (broad s, 2H), 3.78 (broad s, 2H), 3.87 (d,d, J = 5.9, 9.1 Hz, 1H), 4.09 (t, J = 9.2 Hz, 1H), 4.22 (s, 2H), 4.41 (m, 2H), 4.61 (s, 2H), 4.84 (m, 1H), 6.88 (t, J = 9.1 Hz, 1H), 7.02 (m, 1H), 7.35 (m, 6H), 7.82 (t, J = 8.0 Hz, 1H), 8.23 (m, 1H), 8.53 (m, 1H), 8.73 (m, 1H); MS(ES) m/z 629 ($M+H^+$).

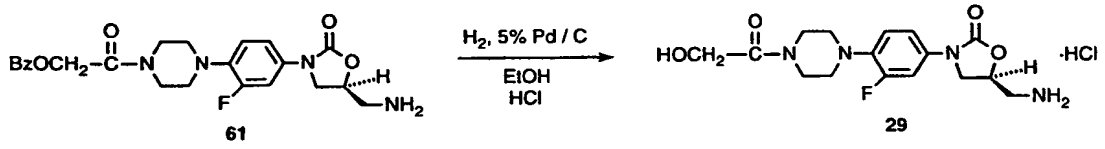
4.



77 61

A solution of **77** (3.36 g, 5.34 mmol) in a mixture of acetonitrile (90 mL), isopropanol (90 mL) and concentrated ammonium hydroxide (90 mL) was warmed at 40-45 °C for 18 h, treated with additional ammonium hydroxide (30 mL), warmed at 40-45 °C for 8 h, treated with additional ammonium hydroxide (25 mL) and warmed at 45 °C for 18 h. It was then mixed with water and extracted with CH_2Cl_2. The extract was washed with dilute NaCl, dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with 5% MeOH-0.5% NH_4OH-$CHCl_3$ gave 2.44 g of **61**: ^{1}H NMR (300 MHz, $CDCl_3$) d 1.50 (broad s), 3.04 (m, 6H), 3.65 (broad s, 2H), 3.81 (m, 3H), 3.99 (t, 1H), 4.21 (s, 2H), 4.61 (s, 2H), 4.66 (m, 1H), 6.88 (t, 1H), 7.12 (m, 1H), 7.33 (m, 5H), 7.47 (d,d, 1H); MS(ES) m/z 443 ($M+H^+$).

5.



61 29

A solution of **61** (1.45 g, 3.3 mmol) and 1.0 N HCl (3.65 mL) in 95% EtOH (150 mL) was treated with 5% palladium-on-carbon catalyst (500 mg) and hydrogenated at an initial pressure of 54 psi for 20 h 15 min. Additional 1.0 N HCl (0.5 mL) and catalyst (100 mg) were added and hydrogenation was continued for 20 h 30 min at an initial pressure of 60 psi. The reaction was compete by TLC; it was neutralized with concentrated NH_4OH, filtered and concentrated in vacuo to give 1.18 g of **29**: ^{1}H NMR [300 MHz, $(CD_3)_2SO$] d 2.94 (broad s, 4H), 3.19 (m, 2H), 3.48 (broad s, 2H),

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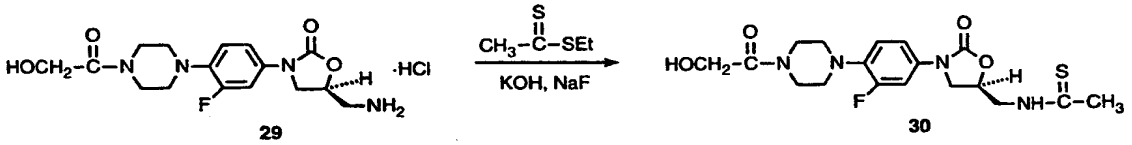
3.60 (broad s, 2H), 3.84 (m, 1H), 4.14 (m, 3H), 4.66 (broad s, 1H), 4.93 (m, 1H), 7.07 (t, 1H), 7.16 (d,d, 1H), 7.48 (d,d, 1H), 8.04 (broad s); IR (mull) 3420, 3099, 3040, 3008, 1755, 1641 cm^{-1}; MS(ES) *m/z* 353 ($M+H^+$). Anal. calcd for $C_{16}H_{22}ClFN_4O_4$: C, 49.42; H, 5.70; Cl, 9.12; N, 14.41. Found: C, 48.16; H, 5.82; Cl, 10.00; N, 14.28.

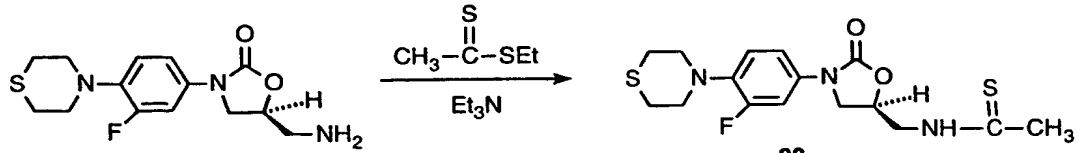
6.



29 30

A stirred mixture of ethyl dithioacetate (180 mL, 1.56 mmol), sodium fluoride (72 mg, 1.7 mmol), **29** (500 mg, 1.29 mmol) and EtOH (70 mL) under nitrogen, was treated with 0.97M KOH (1.46 mL, 1.42 mmol) and the resulting solution was kept at ambient temperature for 3 h 35 min, diluted with $CHCl_3$, washed with water and dilute NaCl, dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with 5% MeOH-0.5% NH_4OH-$CHCl_3$ and crystallization of the resulting product from absolute EtOH gave 0.238 mg (44.9%) **30**: mp 163-165 °C; ^1H NMR (300 MHz, $CDCl_3$) d 2.60 (s, 3H), 3.06 (m, 4H), 3.45 (m, 2H), 3.61 (m, 1H), 3.82 (m, 3H), 4.07 (m, 2H), 4.25 (m, 3H), 4.97 (m, 1H), 6.91 (t, 1H), 7.07 (m, 1H), 7.45 (d,d, 1H), 7.91 (broad s, 1H); MS(FAB) *m/z* (relative intensity) 411 ($M+H^+$, 100), 410 (M^+, 66.5), 266 (3.1); IR 3292, 1733, 1653 cm^{-1}. Anal. calcd for $C_{18}H_{23}FN_4O_4S$: C, 52.67; H, 5.65; N, 13.65. Found: C, 52.76; H, 5.58; N, 13.64.

EXAMPLE 26: **(*S*)-N-[[3-[3-Fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thio-acetamide (32).**



31 32

An ice cold, stirred mixture of **31** (0.38 g, 0.0012 mol) and triethylamine (0.38 mL, 0.0027 mol) in THF (12 mL), under nitrogen, was treated with ethyl dithioacetate (0.16 mL, 0.0014 mol) and then kept at ambient temperature for 24.5 h and concentrated in vacuo. A solution of the residue in CH_2Cl_2 was washed with

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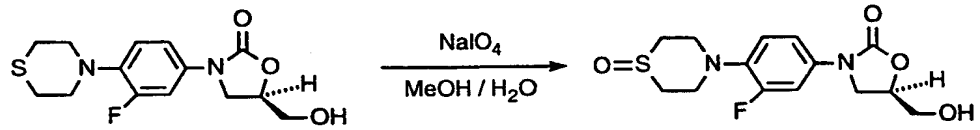
saturated $NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated. Crystallization of the residue from EtOAc-hexane gave 0.355 g of **32**: mp 155-156 °C; MS(ES) *m/z* 370 ($M+H^+$), 392 ($M+Na^+$); IR (DRIFT) 3206, 3042, 1759, 1738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) d 2.60 (s, 3H), 2.95 (s, 4H), 3.43 (m, 4H), 3.82 (d, d, 1H), 4.08 (m, 2H), 4.27 (m, 1H), 4.98 (m, 1H), 7.06 (m, 1H), 7.33 (broad s, 1H), 7.51 (d, 1H), 8.03 (broad s, 1H). Anal. calcd for $C_{16}H_{20}FN_3O_2S_2$: C, 52.01; H, 5.46; N, 11.37. Found: C, 51.86; H, 5.43; N, 11.20.

EXAMPLE 27: **(*S*)-N-[[3-[3-Fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thio-acetamide, thiomorpholine S-oxide (34).**

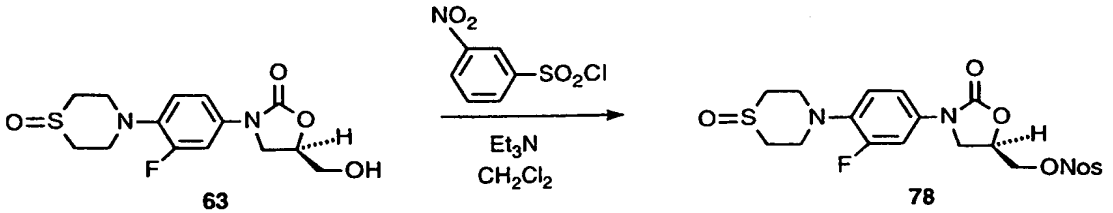
1.



62 63

An ice cold, stirred mixture of sodium metaperiodate (1.08 g, 5.05 mmol) and water (12 mL), under nitrogen, was treated with **62**[16] (1.5 g, 4.8 mmol) and MeOH (17 mL) and kept at 6 °C for 18 h and at 4 °C for 3 h. It was then treated with additional sodium metaperiodate (0.1 g), kept at 4°C for 3 h and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and concntrated to give 1.4 g of **63**: ^1H NMR [300 MHz, $(CD_3)_2SO$] d 2.84 (m, 2H), 3.01 (m, 2H), 3.16 (m, 2H), 3.50 (m, 3H), 3.65 (m, 1H), 3.77 (d,d, 1H), 4.03 (t, 1H), 4.66 (m, 1H), 5.18 (t, 1H), 7.16 (m, 2H), 7.52 (m, 1H); MS(ES) *m/z* 329 ($M+H^+$), 351 ($M+Na^+$).

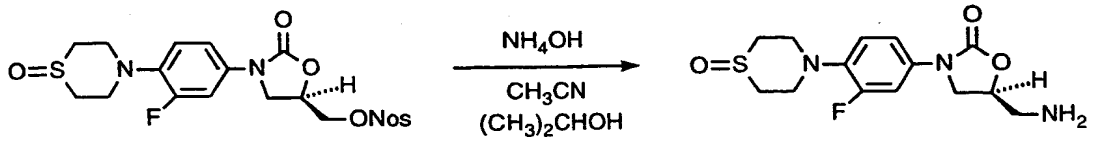
2.



63 78

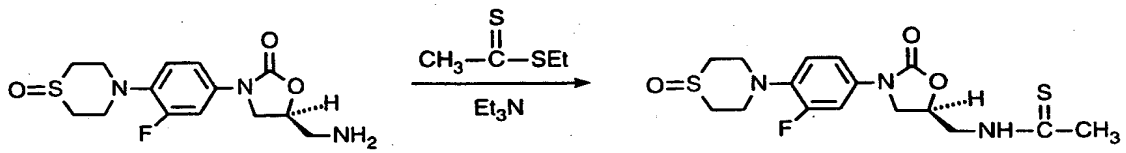
An ice cold, stirred mixture of **63** (1.27 g, 3.87 mmol) and triethylamine (0.732 mL, 5.25 mmol) in CH_2Cl_2 (130 mL), under nitrogen, was treated with *m*-nitrobenzenesulfonyl chloride (1.15 g, 5.19 mmol) and kept at ambient temperature for about 24 h. It was diluted with CH_2Cl_2, washed with water and brine, dried (Na_2SO_4) and concentrated to give **78** which was used in the next reaction without

purification.

3. 

78 33

A stirred mixture of the product (**78**) from the previous reaction, acetonitrile (70 mL) and isopropanol (70 mL) was treated with concentrated ammonium hydroxide (70 mL, 29.9% NH_3) and kept at 40 °C for 2 h, at ambient temperature for 18 h and at 40-45 °C for 4 h; it was concentrated to about 50 mL, diluted with water and extracted with CH_2Cl_2. The extracts were washed with water and brine, dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel with 5% MeOH-$CHCl_3$ gave 0.58 g of **33**: MS(ES) *m/z* 328 ($M+H^+$), 350 ($M+Na^+$); ^1H NMR [300 MHz, $(CD_3)_2SO$] d 2.81 (m, 4H), 3.01 (m, 2H), 3.16 (m, 2H), 3.30 (broad s), 3.49 (m, 2H), 3.80 (d,d, 1H), 4.01 (t, 1H), 4.58 (m, 1H), 7.19 (m, 2H), 7.51 (m, 1H).

4. 

33 34

A stirred suspension of **33** (3.7 g, 0.011 mol) and triethylamine (3.5 mL, 0.025 mol) in THF (120 mL) was cooled, in an ice bath, under nitrogen, treated, dropwise during 2 min, with a solution of ethyl dithioacetate (1.47 mL, 0.0128 mol) in THF (2 mL) and kept at ambient temperature for 22 h. The resulting solution was concentrated and the residue crystallized from acetonitrile to give 3.61 g of **34**: mp 176-177 °C ; ^1H NMR [300 MHz, $(CD_3)_2SO$] d 2.42 (s, 3H), 2.85 (m, 2H), 3.01 (m, 2H), 3.18 (m, 3H), 3.50 (m, 2H), 3.78 (d,d, 1H), 3.89 (broad s, 2H), 4.12 (t, 1H), 4.92 (m, 1H), 7.18 (m, 2H), 7.49 (m, 1H), 10.33 (s, 1H); IR (DRIFT) 3186, 3102, 1741 cm^{-1}; MS(ES) *m/z* 386 ($M+H^+$), 408 ($M+Na^+$). Anal. calcd for $C_{16}H_{20}FN_3O_3S_2 \cdot 0.5 H_2O$: C, 48.71; H, 5.37; N, 10.65; S, 16.26; H_2O, 2.38. Found: C, 48.75; H, 5.17; N, 10.72; S, 16.07; H_2O, 1.72.

EXAMPLE 28: **(*S*)-N-[[3-[3-Fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-**

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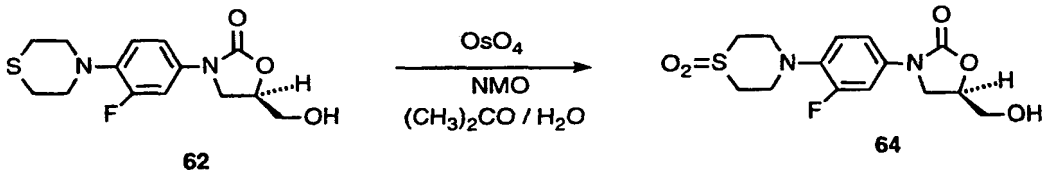
oxazolidinyl]methyl]thio-acetamide, thiomorpholine S, S-dioxide (36).

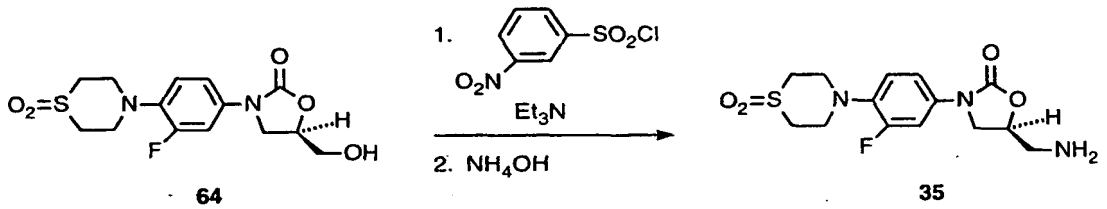
1.



62 64

A stirred mixture of **62**[16] (0.399 g, 0.00128 mol) in 25% water/acetone (12 mL), under nitrogen was treated with N-methylmorpholine, N-oxide (0.45 g, 0.00384 mol) and 0.1 mL of a 2.5 wt% solution of osmium tetroxide in *tert*-butanol. It was kept at ambient temperature for 18 h, mixed with saturated $NaHSO_3$ (50 mL) and extracted with CH_2Cl_2. The extract was washed with saturated $NaHSO_3$ and brine, dried (Na_2SO_4) and concentrated. The residue was mixed with 3.5% MeOH-CH_2Cl_2 and filtered; the solid was dissolved in 15% MeOH-CH_2Cl_2 and concentrated to give 0.29 g of **64**. The filtrate was chromatographed on silica gel with 3.5% MeOH-CH_2Cl_2 to give 0.1 of additional **64**: MS(ES) *m/z* 345 ($M+H^+$), 367 ($M+Na^+$); ^1H NMR [300 MHz, $(CD_3)_2SO$] d 3.26 (m, 4H), 3.44 (m, 4H), 3.60 (m, 2H), 3.80 (d,d, 1H), 4.05 (t, 1H), 4.69 (m, 1H), 7.22 (m, 2H), 7.54 (d, 1H).

2.

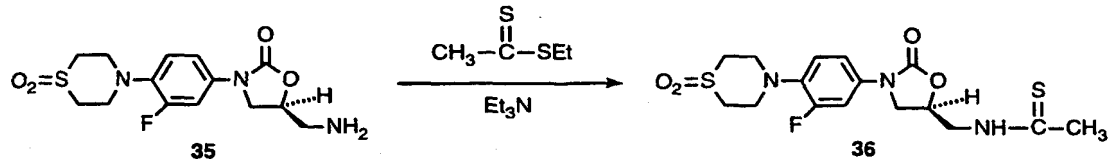


64 35

A stirred mixture of **64** (0.39 g, 0.00113 mol) and triethylamine (0.214 mL, 0.00154 mol) in CH_2Cl_2 (37 mL) was cooled, under nitrogen, in an ice bath and treated, portionwise during 5 min, with 3-nitrobenzenesulfonyl chloride (0.335 g, 0.00151 mol). The mixture was kept in the ice bath for 20 min and at ambient temperature for 18 h and concentrated in vacuo. A stirred solution of the residue in 2-propanol (25 mL) and acetonitrile (25 mL), under nitrogen, was treated with 30% NH_4OH (25 mL), warmed at 50-55 °C for 6 h and kept at ambient temperature for 48 h. It was concentrated to remove the organic solvents, diluted with water and extracted with CH_2Cl_2. The extract was washed with water and brine, dried ($MgSO_4$) and

concentrated. Flash chromatography of the residue on silica gel with 6% MeOH-0.4% NH_4OH-$CHCl_3$ gave 0.29 g of **35**: ^1H NMR [300 MHz, $(CD_3)_2SO$] d 1.59 (broad s, 2H), 2.78 (m, 2H), 3.24 (m, 4H), 3.43 (m, 4H), 3.81 (d,d, 1H), 4.01 (t, 1H), 4.57 (m, 1H), 7.18 (m, 2H), 7.52 (m, 1H); MS(ES) *m/z* 344 ($M+H^+$), 366 ($M+Na^+$).

3.

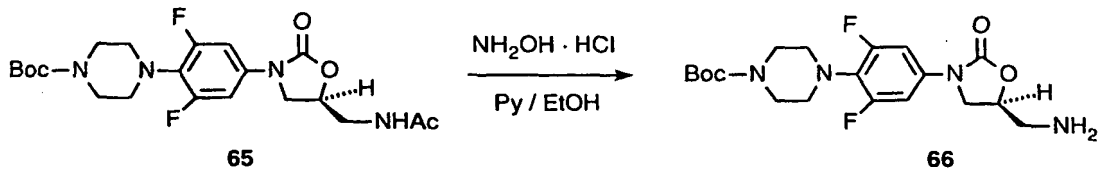


35 36

A stirred, ice cold suspension of **35** (0.28 g, 0.85 mmol) in a mixture of Et_3N (0.26 mL, 1.9 mmmol) and THF (10 mL) was treated with ethyl dithioacetate (0.11 mL, about 6 drops) and kept in the ice bath for 20 min and then at ambient temperature; the reaction was followed by TLC. After 20 h there was still a suspension and only partial reaction; additional THF (10 mL) and ethyl dithioacetate (3 drops) were added. After an additional 48 h the reaction was still incomplete; the suspension was treated with CH_2Cl_2 (10 mL) and kept for 72 h. At this time almost complete solution and an almost complete conversion to product had been obtained. An additional drop of ethyl dithioacetate was added and the mixture was kept at ambient temperature for 5 d and concentrated in vacuo. The residue was mixed with EtOAc, washed with saturated $NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated. Crystallization of the residue from MeOH-EtOAc gave 0.209 g of **36**: mp 197-198 °C; ^1H NMR [300 MHz, $(CD_3)_2SO$] d 2.42 (s, 3H), 3.24 (m, 4H), 3.43 (m, 4H), 3.78 (d,d, 1H), 3.88 (m, 2H), 4.12 (t, 1H), 4.92 (m, 1H), 7.18 (m, 2H), 7.50 (m, 1H), 10.37 (broad s, 1H); IR (mull) 3300, 3267, 1743 cm^{-1}; MS(ES) *m/z* 424 ($M+Na^+$). Anal. calcd for $C_{16}H_{20}FN_3O_4S_2$: C, 47.87; H, 5.02; N, 10.47. Found: C, 47.84; H, 5.23; N, 10.28.

EXAMPLE 29: **(*S*)-N-[[3-[3,5-Difluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide (38).**

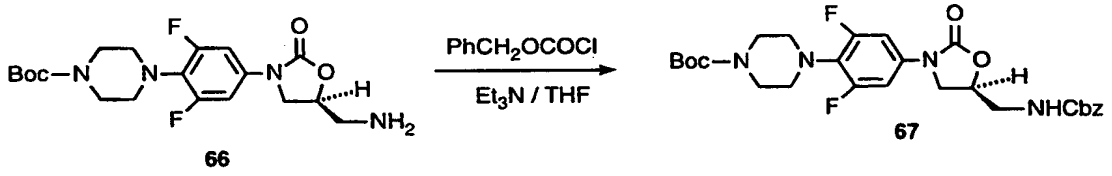
1.



65 66

A stirred mixture of **65**[17,18] (1.8 g, 0.00396 mol), pyridine (30 mL) and absolute EtOH (3 mL), under nitrogen, was treated with hydroxylamine hydrochloride (1.44 g, 0.0207 mol), warmed to the reflux temperature during 2 h, refluxed for 3.5 h, kept at ambient temperature for 18 h and at reflux for 4 h. It was concentrated in vacuo and the residue was mixed with water, adjusted to pH 11 with saturated $NaHCO_3$ and extracted with Et_2O. The extracts were washed with brine, dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with 5% MeOH-0.35% NH_4OH-$CHCl_3$ gave 0.75 g of recovered **65** and 0.72 g of **66**: ^1H NMR [300 MHz, $(CD_3)_2SO$] d 1.40 (s, 9H), 1.72 (broad s, 2H), 2.78 (m, 2H), 2.97 (m, 4H), 3.40 (m, 4H), 3.80 (d,d, 1H), 4.00 (t, 1H), 4.59 (m, 1H), 7.27 (d, 2H); MS(ES) *m/z* 413 ($M+H^+$), 435 ($M+Na^+$).

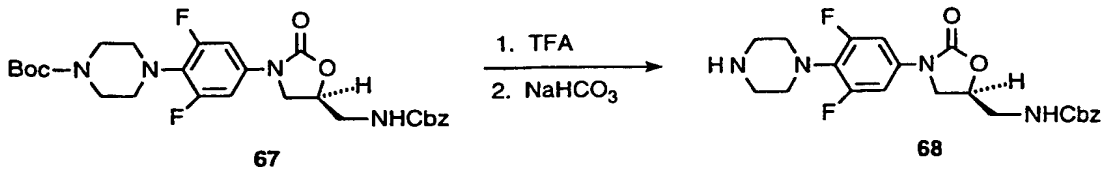
2.



66 **67**

An ice cold, stirred mixture of **66** (0.75 g, 0.0018 mol) and triethylamine (0.315 mL, 0.00225 mol) in THF (12 mL), under nitrogen, was treated, dropwise with benzyl chloroformate (0.29 mL, 0.0020 mol), kept in the ice bath for 15 min and at ambient temperature for 2 h and concentrated in vacuo. The residue was mixed with CH_2Cl_2 and washed with saturated $NaHCO_3$, water and brine, dried (Na_2SO_4) and concentrated. This residue was mixed with Et_2O and filtered to give 0.939 g of **67**: mp 116-118 °C; ^1H NMR (300 MHz, $CDCl_3$) d 1.48 (s, 9H), 3.08 (m, 4H), 3.53 (m, 4H), 3.60 (m, 2H), 3.73 (m, 1H), 3.96 (t, 1H), 4.76 (m, 1H), 5.10 (s, 2H), 5.21 (m, 1H),7.07 (d, 2H), 7.31 (s, 5H); MS(ES) *m/z* 547 ($M+H^+$), 569 ($M+Na^+$).

3.



67 **68**

Compound **67** (0.805 g, 0.00147 mol) was added with stirring, portionwise during 5 min, under nitrogen, to ice cold trifluoroacetic acid (9 mL). The resulting solution was kept in the ice bath for 1 h and then concentrated under a stream of nitrogen.

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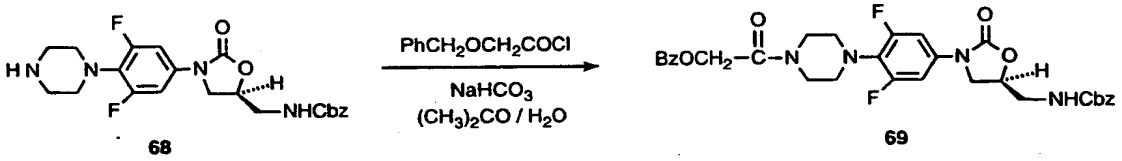
The residue was mixed with ice and saturated $NaHCO_3$ and extracted with CH_2Cl_2; the extract was washed with water and brine, dried (Na_2SO_4) and concentrated to give 0.63 g of product. The combined aqueous layer was reextracted with EtOAc; the extracts were washed with water and brine, dried (Na_2SO_4) and concntrated to give additional product. The combined product amounted to 0.68 g of **68** which was used in the next reaction without further purification.

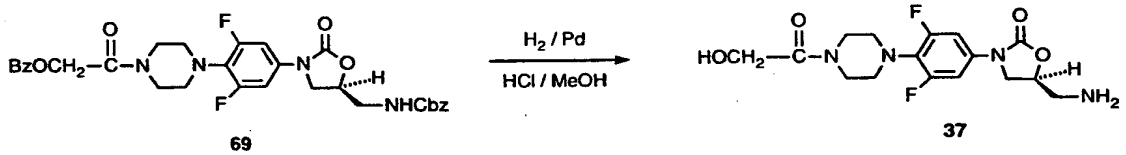
4.



68 69

An ice cold, stirred mixture of **68** (0.68 g, 0.00152 mol), saturated $NaHCO_3$ (15.2 mL) and acetone (40 mL), under nitrogen was treated, dropwise during 15 min, with a solution of benzyloxyacetyl chloride (0.29 mL, 0.0019 mol) in acetone (5 mL), kept at ambient temperature for 6 h, diluted with EtOAc and washed with water and brine. The extract was dried ($MgSO_4$) and concentrated in vacuo to give 0.72 g of **69**: MS(ES) *m/z* 395 ($M+H^+$), 617 ($M+Na^+$); ^1H NMR (300 MHz, $CDCl_3$) d 3.12 (m, 4H), 3.59 (m, 4H), 3.74 (m, 3H), 3.96 (t, 1H), 4.22 (s, 2H), 4.62 (s, 2H), 4.75 (broad s, 1H), 5.10 (s, 2H), 5.22 (m, 1H), 7.08 (d, 2H), 7.33 (m, 10H).

5.



69 37

A mixture of **69** (0.72 g, 0.0012 mol), MeOH and 5% palladium-on-carbon catalyst (0.4 g) was hydrogenated at an initial pressure of 45 psi for 4 h. By TLC (8% MeOH-0.5% NH_4OH-$CHCl_3$) the starting material had been reduced and two products formed. 1M Hydrochloric acid (1.34 mL) was added and hydrogenation was continued at an initial pressure of 40 psi for 21 h. By TLC only the more polar product remained. The catalyst was removed by filtration and the filtrate was concentrated to give 0.40 g of **37**: MS(ES) *m/z* 371 ($M+H^+$), 393 ($M+Na^+$); ^1H NMR [300 MHz, $(CD_3)_2SO$] d 3.02 (s, 4H), 3.20 (m, 2H), 3.43 (s, 2H), 3.56 (s, 2H), 3.84 (m,

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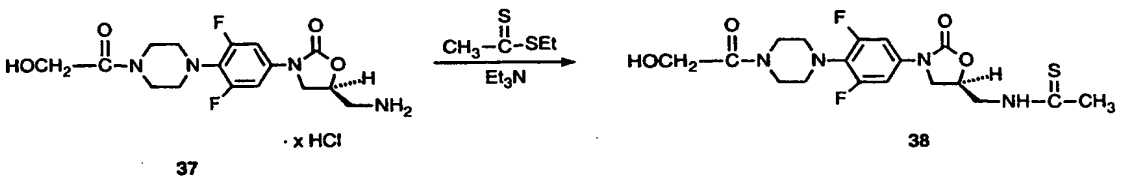
1H), 3.84 (broad s), 4.10 (s, 2H), 4.14 (t, 1H), 4.96 (m, 1H), 7.26 (d, 2H), 8.41 (broad s, 3H).

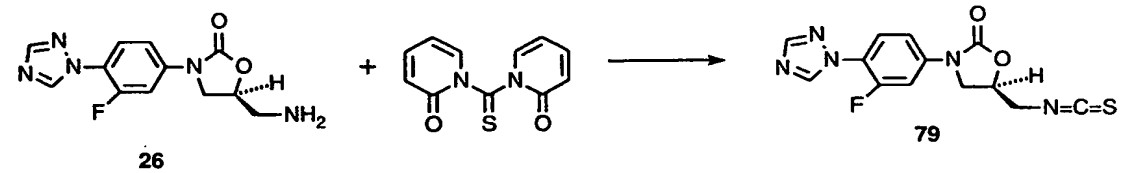
6.



A stirred suspension of **37** (0.38 g) in a solution of Et_3N (0.31 mL) and THF (10 mL), under nitrogen, was treated with ethyl dithioacetate (0.13 mL, about 7 drops) and kept at ambient temperature for 7 d; the reaction was followed by TLC (8% MeOH-0.5% NH_4OH-$CHCl_3$). Additional ethyl dithioacetate (2 drops) was added after 24 h; after 30 h CH_2Cl_2 (10 mL) and ethyl dithioacetate (3 drops) were added; after 48 h additional triethylamine (0.3 mL) was added. The mixture was concentrated in vacuo and the residue was mixed with ice and saturated $NaHCO_3$ an extracted with CH_2Cl_2. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel with 2.5% MeOH-CH_2Cl_2 and the product was crystallized from MeOH to give 0.182 g of **38**: mp 110-111 °C (dec); MS(ES) *m/z* 429 ($M+H^+$), 451 ($M+Na^+$); HRMS (FAB) calcd for $C_{18}H_{23}F_2N_4O_4S$ ($M+H^+$) 429.1408, found 429.1415; IR (DRIFT) 1760, 1652, 1639 cm^{-1}; $[\alpha]^{24}_D$ 8° (MeOH).

EXAMPLE 30: **(*S*)-N-[[3-[4-[1-[1,2,4]Triazolyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea (44).**

1.



A solution of **26** (0.190 g, 0.685 mmol) in CH_2Cl_2 (20 mL) was added, dropwise during 20 min, under nitrogen, to an ice cold, stirred solution of 1,1¢-thiocarbonyldi-2(1H)-pyridone (0.193 g, 0.831 mmol) in CH_2Cl_2 (7 mL). The mixture was kept in the ice bath for 20 min and at ambient temperature for 2 h, diluted with CH_2Cl_2,

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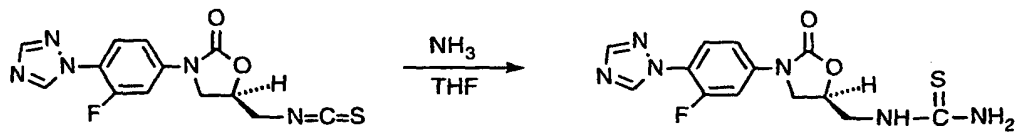
washed with water and brine, dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel with 10-15% CH_3CN-CH_2Cl_2 gave 0.11 g of **79** which was used in the next reaction without further purification: MS(ES) *m/z* 320 ($M+H^+$), 342 ($M+Na^+$).

2.

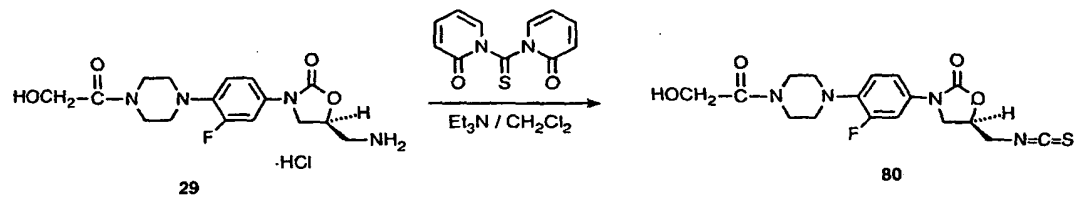


79 **44**

A stirred, ice cold solution of **79** (0.10 g, 0.31 mmol) in THF (15 mL) was treated with excess anhydrous ammonia and kept in the ice bath for 90 min. It was then evaporated under a stream of nitrogen to a volume of about 5 mL to give a solid which was collected by filtration and washed with cold THF to give 0.105 g of **44**: mp 214-215 °C; ^1H NMR [300 MHz, $(CD_3)_2SO$] d 3.82 (m, 3H), 4.18 (t, 1H), 4.89 (broad s, 1H), 7.20 (broad s, 2H), 7.50 (d, 1H), 7.79 (m, 2H), 7.93 (t, 1H), 8.26 (s, 1H), 8.97 (s, 1H); MS(ES) *m/z* 337 ($M+H^+$), 359 ($M+Na^+$). Anal. calcd for $C_{13}H_{13}FN_6O_2S$: C, 46.42; H, 3.90; N, 24.99. Found: C, 46.22; H, 3.98; N, 24.55.

EXAMPLE 31: **(*S*)-N-[[3-[3-Fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]-methyl]thiourea (45).**

1.



29 **80**

An ice cold, stirred solution of 1,1¢-thiocarbonyl-2(1H)-dipyridone (0.123 g, 0.530 mmol) in CH_2Cl_2 (5 mL), under nitrogen, was treated with a suspension of **29** (0.17 g, 0.4 mmol) in CH_2Cl_2 (20 mL) and then during 10 min with a solution of triethylamine (0.111 mL, 0.8 mmol) in CH_2Cl_2 (10 mL). It was kept in the ice bath for 30 min, at ambient temperature for 2 h and at < 0 °C for 18 h. It was then diluted with CH_2Cl_2, washed with water and brine, dried ($MgSO_4$) and concentrated. The residue (**80**) was used without further purification in the next

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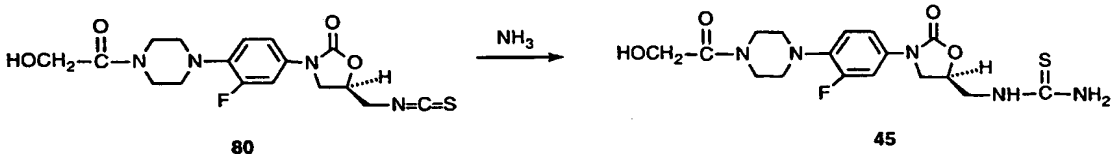
reaction. A sample of **80** that was purified by flash chromatography on silica gel with 10-20% acetonitrile-CH_2Cl_2 had: ^{1}H NMR (300 MHz, $CDCl_3$) d 1.60 (broad s), 3.07 (m, 4H), 3.45 (m, 2H), 3.85 (m, 4H), 3.97 (d,d, 1H), 4.16 (t, 1H), 4.21 (s, 2H), 4.82 (m, 1H), 6.95 (t, 1H), 7.13 (d,d, 1H), 7.47 (d,d, 1H); MS *m/z* 395 ($M+H^+$); 417 ($M+Na^+$).

2.

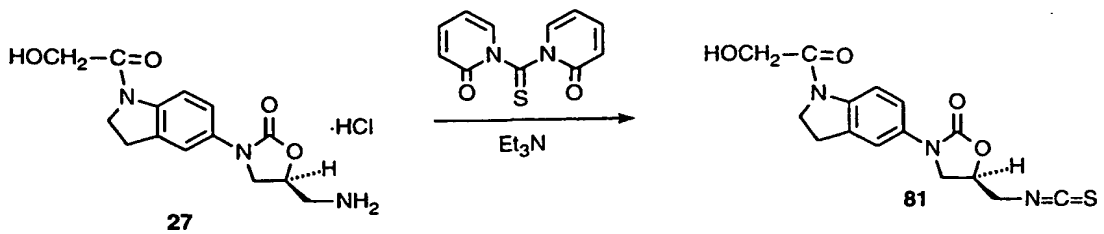


80 45

Excess anhydrous ammonia was bubbled into a stirred, ice cold solution of **80** (crude product from the previous reaction) in THF (25 mL) and the mixture was kept in the ice bath for 90 min and concentrated under a stream of nitrogen. The residue was chromatographed on silica gel with 5% MeOH-0.4% NH_4OH-$CHCl_3$ and the product was crystallized from acetonitrile to give 0.0544 g of **45**: mp 209-210 °C; ^{1}H NMR [300 MHz, $(CD_3)_2SO$] d 294 (broad s, 4H), 3.47 (broad s, 2H), 3.60 (broad s, 2H), 3.78 (broad s, 3H), 4.07 (t, 1H), 4.10 (d, J = 5.5 Hz, 2H), 4.63 (t, J = 5.5 Hz, 1H), 4.81 (broad s, 1H), 7.05 (t, 1H), 7.16 (d,d, 1H), 7.15 (broad s, 2H), 7.49 (d,d, 1H), 7.91 (t, 1H); IR (mull) 3443, 3403, 3321, 3202, 3081, 1753, 1655, 1648 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{23}FN_5O_4S$ ($M+H^+$) 412.1454, found 412.1447. Anal. calcd for $C_{17}H_{22}FN_5O_4S$: C, 49.63; H, 5.39; N, 17.02. Found: C, 49.63; H, 5.48; N, 16.99.

EXAMPLE 32: **(S)-N-[[3-[1-(Hydroxyacetyl)-5-indolinyl]-2-oxo-5-oxazolidinyl]methyl]thiourea (46).**

1.



27 81

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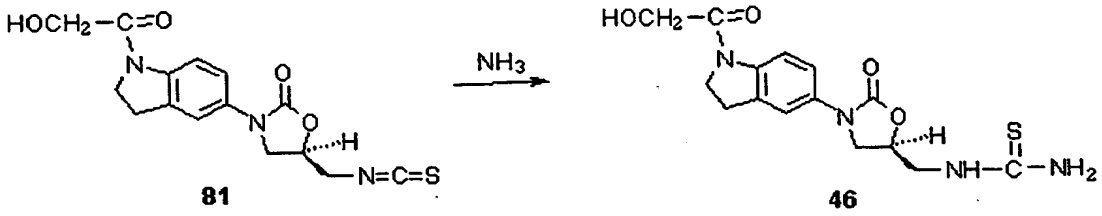
An ice cold, stirred solution of 1,1¢-thiocarbonyldi-2(1H)-pyridone (0.096 g, 0.41 mmol) in CH_2Cl_2 (5 mL) was treated with a suspension of **27** (0.10 g, 0.34 mmol) in CH_2Cl_2 (15 mL) and then with 0.05 mL (0.36 mmol) of triethylamine. It was kept in the ice bath for 30 min and at ambient temperature for 2 h, diluted with CH_2Cl_2, washed with water and brine, dried ($MgSO_4$) and concentrated. Chromatography ofthe residue on silica gel with 20-40% CH_3CN-CH_2Cl_2 gave 0.04 g of **81**.

2.

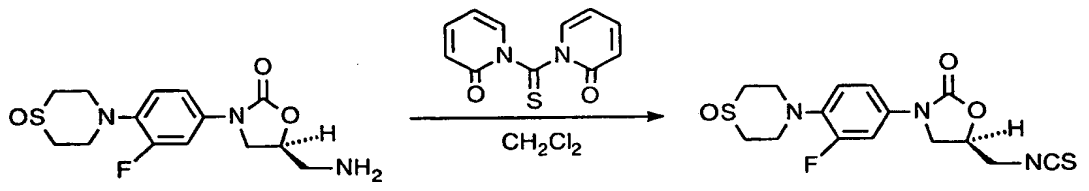


81 **46**

Excess anhydrous ammonia was bubbled into an ice cold solution of **81** (0.04 g) in THF (30 mL) and the mixture was kept in the ice bath for 80 min and concentrated under a stream of nitrogen. The residue was crystallized from CH_3CN to give 0.0151 g of **46**: mp 214-215 °C (dec); MS (FAB) *m/z* 351 ($M+H^+$), 350 (M^+), 319, 304, 147; HRMS (FAB) calcd for $C_{15}H_{19}N_4O_4S$ ($M+H^+$) 351.1127, found 351.1130; IR (DRIFT) 3329, 3296, 3196, 1746, 1655, 1626 cm^{-1}.

EXAMPLE 33: **(*S*)-N-[[3-[3-Fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea, thiomorpholine S-oxide (47).**

1.



33 **82**

A suspension of **33** (0.30 g, 0.92 mmol) in CH_2Cl_2 (7 mL) was added, during 20 min, to an ice cold, stirred mixture of 1,1¢-thiocarbonyldi-2(1H)-pyridone (0.258 g, 1.11 mmol) and CH_2Cl_2 (20 mL). The mixture was kept in the ice bath for 20 min and at ambient temperature for 2 h, mixed with CH_2Cl_2 (50 mL), washed with water and brine, dried ($MgSO_4$) and concentrated. Chromatography of the product on silica gel with 20-50% CH_3CN-CH_2Cl_2 gave 0.27 g of **82** which was used in the next reaction: MS(ES) *m/z* 370 ($M+H^+$), 392 ($M+Na^+$).

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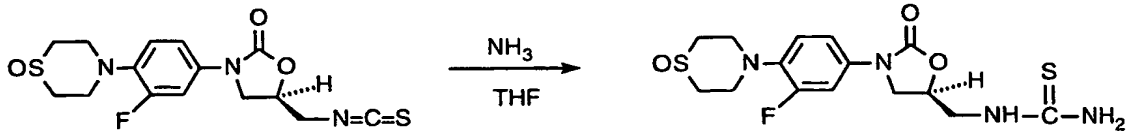
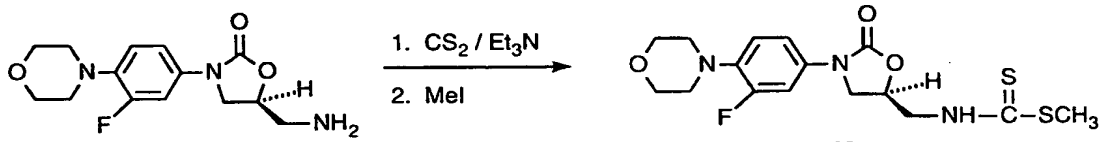
2.



82 47

A stirred, ice cold solution of **82** (0.27g , 0.73 mmol) in THF (15 mL), under nitrogen, was treated with excess anhydrous ammonia, kept in the ice bath for 1 h and concentrated; crystallization of the residue from MeOH gave 0.175 g of **47**; mp 212-213 °C; ^{1}H NMR [300 MHz, $(CD_3)_2SO$] d 2.83 (m, 2H), 3.01 (m, 2H), 3.17 (m, 2H), 3.50 (t, 2H), 3.78 (broad s, 3H), 4.08 (t, 1H), 4.80 (broad s, 1H), 7.17 (m, 2H), 7.17 (broad s, 2H), 7.50 (d, 1H), 7.90 (t, 1H); MS(ES) *m/z* 409 ($M+Na^+$); IR (mull) 3335, 3284, 3211, 3175, 3097, 1750, 1630 cm^{-1}. Anal. calcd for $C_{15}H_{19}FN_4O_3S_2$: C, 46.62; H, 4.95; N, 14.50. Found: C, 46.50; H, 4.95; N, 14.40.

EXAMPLE 34: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl-S-methyldithiocarbamate (48).**



39 48

An ice cold, stirred mixture of **39**[8] (0.59 g, 0.0020 mol), EtOH (1.5 mL), water (2 drops) and triethylamine (0.613 mL, 0.00440 mol), under nitrogen, was treated with carbon disulfide (0.066 mL, 0.0011 mol) and kept in the ice bath for 2 h and at ambient temperature for 18 h. (A solution was obtained after the addition of carbon disulfide; a white precipitate began to form soon after the mixture was warmed to ambient temperature.) The thick suspension was treated, dropwise during 2 min, with a solution of methyl iodide (0.137 mL, 0.00220 mol) in EtOH (2 mL) and the mixture was kept at ambient temperature for 1.5 h and concentrated in vacuo. A solution of the residue in EtOAc was washed with saturated $NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel with 1.8% MeOH-CH_2Cl_2 and the product was crystallized from EtOAc to give 0.197 g of **48**: mp 154-155 °C; IR (mull) 3354, 3346, 1726 cm^{-1}. Anal. calcd for $C_{16}H_{20}FN_3O_3S_2$: C, 49.85; H, 5.23; N, 10.90. Found: C, 49.73; H, 5.25; N, 10.82.

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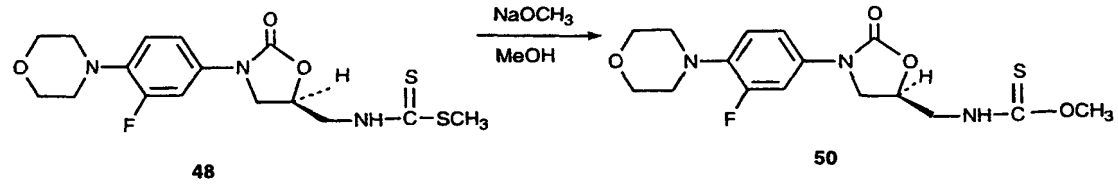
EXAMPLE 35: **(*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)ph nyl]-2-oxo-5-oxazolidinyl]methyl-O-methylthiocarbamate (50).**



48 50

A stirred mixture of **48** (0.200 g, 0.518 mmol), sodium methoxide (0.003 g, 0.06 mmol) and MeOH (5 mL), under nitrogen, was refluxed for 4 h and kept at ambient temperature for 18 h. It was found that the starting material and product had similar mobilities on TLC. the reaction was therefore followed by MS(ES). Starting material was still present. The mixture was refluxed for 3 h, additional sodium methoxide (0.005 g) was added and reflux was continued for 2 h. It was kept at ambient temperature for 18 h, refluxed for 1 h, kept at ambient temperature 1.5 h and concentrated in vacuo. The residue was mixed with ice, the pH was adjusted to 9-10 with 1M $KHSO_4$ and saturated $NaHCO_3$ and the mixture was extracted with CH_2Cl_2. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel with 5% acetone-CH_2Cl_2 and the product was crystallized from EtOAc-hexane to give 0.107 g of **50**: mp 128-129 °C; MS(ES) *m/z* 370 ($M+H^+$), 392 ($M+Na^+$); IR (DRIFT) 3282, 3251, 1753, 1735 cm^{-1}; ^1H NMR [300 MHz, $(CD_3)_2SO$] d 2.94 (m, 4H), 3.47, 374 (m,m, 7H), 3.86, 3.91 (s,s, 3H), 4.10 (m, 1H), 4.73, 4.86 (m,m, 1H), 7.05 (t, 1H), 7.16 (d,d, 1H), 7.47 (d,d, 1H), 9.41, 9.50 (s,s, 1H). Anal. calcd for $C_{16}H_{20}FN_3O_4S$: C, 52.02; H, 5.46; N, 11.38. Found: C, 51.97; H, 5.49; N, 11.35.

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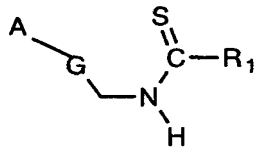
WHAT IS CLAIMED:

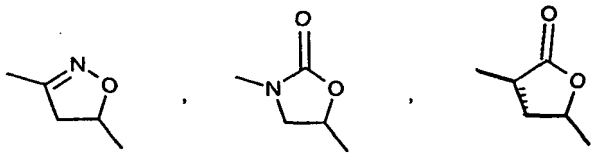
1. A compound of the formula I



I

or pharmaceutical acceptable salts thereof wherein:

G is



R_1 is

a) H,

b) NH_2,

c) NH-C_{1-4} alkyl,

d) C_{1-4} alkyl,

e) -OC_{1-4} alkyl,

f) -S C_{1-4} alkyl,

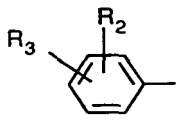
g) C_{1-4} alkyl substituted with 1-3 F, 1-2 Cl, CNor -COOC_{1-4} alkyl,

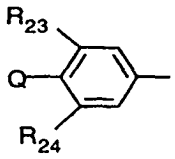
h) C_{3-6} cycloalkyl,

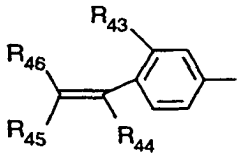
i) N(C_{1-4}) alkyl)$_2$ or

j) N(CH$_2$)$_{2-5}$;

A is

a) 

b)  ,

c)  ,

d) a 5-membered heteroaromatic moiety having one to three atoms selected from the group consisting of S, N, and O,

wherein the 5-membered heteroaromatic moiety is bonded via a carbon atom,

wherein the 5-membered heteroaromatic moiety can additionally have a fused-on benzene or naphthyl ring,

wherein the heteroaromatic moiety is optionally substituted with one to three R_{48},

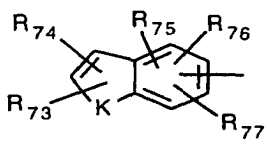
e) a 6-membered heteroaromatic moiety having at least one nitrogen atom,

wherein the heteroaromatic moiety is bonded via a carbon atom,

wherein the 6-membered heteroaromatic moiety can additionally have a fused-on benzene or naphthyl ring,

wherein the heteroaromatic moiety is optionally substituted with one to three R_{55},

f) a β-carbolin-3-yl, or indolizinyl bonded via the 6-membered ring, optionally substituted with one to three R_{55},

g)  , or

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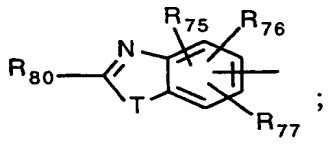
h) 

;

wherein R_2 is

a) H,
b) F,
c) Cl,
d) Br,
e) C_{1-3} alkyl,
f) NO_2, or
g) R_2 and R_3 taken together are -O-$(CH_2)_h$-O-;

R_3 is

a) -S(=O)$_i$ R_4,
b) -S(=O)$_2$-N=S(O)$_j$$R_5$$R_6$,
c) -SC(=O)R_7,
d) -C(=O)R_8,
e) -C(=O)R_9,
f) -C(=O)N$R_{10}$$R_{11}$,
g) -C(=NR_{12})R_8,
h) -C(R_8)(R_{11})-OR_{13},
i) -C(R_9)(R_{11})-OR_{13},
j) -C(R_8)(R_{11})-OC(=O)R_{13},
k) -C(R_9)(R_{11})-OC(=O)R_{13},
l) -N$R_{10}$$R_{11}$,
m) -N(R_{10})-C(=O)R_7,
n) -N(R_{10})-S(=O)$_i$$R_7$,
o) -C(OR_{14})(OR_{15})R_8,
p) -C(R_8)(R_{16})-N$R_{10}$$R_{11}$, or
q) C_{1-8} alkyl substituted with one or more =O other than at alpha position, -S(=O)$_i$$R_{17}$, -N$R_{10}$$R_{11}$, C_{2-5} alkenyl, or C_{2-5} alkynyl;

R_4 is

a) C_{1-4} alkyl optionally substituted with one or more halos, OH, CN, N$R_{10}$$R_{11}$, or -$CO_2$$R_{13}$,

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b) C_{2-4} alkenyl,

c) $-NR_{16}R_{18}$,

d) $-N_3$,

e) $-NHC(=O)R_7$,

f) $-NR_{20}C(=O)R_7$,

g) $-N(R_{19})_2$,

h) $-NR_{16}R_{19}$, or

i) $-NR_{19}R_{20}$,

R_5 and R_6 at each occurrence are the same or different and are

a) C_{1-2} alkyl, or

b) R_5 and R_6 taken together are $-(CH_2)_k-$;

R_7 is C_{1-4} alkyl optionally substituted with one or more halos;

R_8 is

a) H, or

b) C_{1-8} alkyl optionally substituted with one or more halos, or C_{3-8} cycloalkyl;

R_9 is C_{1-4} alkyl substituted with one or more

a) $-S(=O)R_{17}$,

b) $-OR_{13}$,

c) $-OC(=O)R_{13}$,

d) $-NR_{10}R_{11}$, or

e) C_{1-5} alkenyl optionally substituted with CHO;

R_{10} and R_{11} at each occurrence are the same or different and are

a) H,

b) C_{1-4} alkyl, or

c) C_{3-8} cycloalkyl;

R_{12} is

a) $-NR_{10}R_{11}$,

b) $-OR_{10}$; or

c) $-NHC(=O)R_{10}$;

R_{13} is

a) H, or

b) C_{1-4} alkyl;

R_{14} and R_{15} at each occurrence are the same or different and are

a) C_{1-4} alkyl, or

b) R_{14} and R_{15} taken together are $-(CH)_l-$;

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R_{16} is

a) H,

b) C_{1-4} alkyl, or

c) C_{3-8} cycloalkyl;

R_{17} is

a) C_{1-4} alkyl, or

b) C_{3-8} cycloalkyl;

R_{18} is

a) H,

b) C_{1-4} alkyl,

c) C_{2-4} alkenyl,

d) C_{3-4} cycloalkyl,

e) $-OR_{13}$ or

f) $-NR_{21}R_{22}$;

R_{19} is

a) Cl,

b) Br, or

c) I;

R_{20} is a physiologically acceptable cation;

R_{21} and R_{22} at each occurrence are the same or different and are

a) H,

b) C_{1-4} alkyl, or

c) $-NR_{21}R_{22}$ taken together are $-(CH_2)_m-$;

wherein R_{23} and R_{24} at each occurrence are the same or different and are

a) H,

b) F,

c) Cl,

d) C_{1-2} alkyl,

e) CN

f) OH,

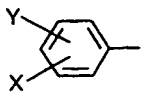
g) C_{1-2} alkoxy,

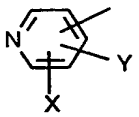
h) nitro, or

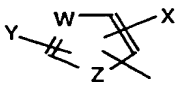
i) amino;

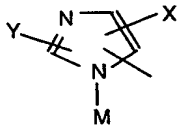
BNSDOCID <WO 9854161A1_IA>

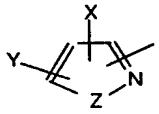
Q is

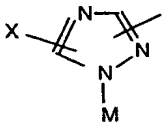
a)  ,

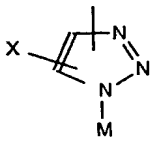
b)  ,

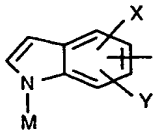
c)  ,

d)  ,

e)  ,

f)  ,

g)  ,

h)  ,

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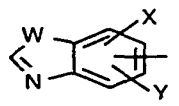
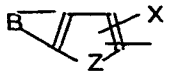
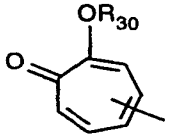
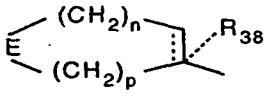
i)  ,

j) 

k)  ,

l)  ,

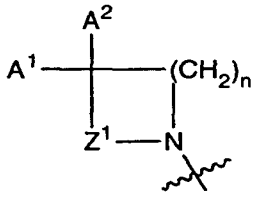
m) a diazinyl group optionally substituted with X and Y,

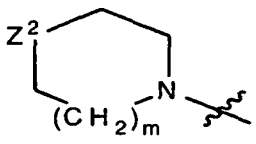
n) a triazinyl group optionally substituted with X and Y,

o) a quinolinyl group optionally substituted with X and Y,

p) a quinoxalinyl group optionally substituted with X and Y,

q) a naphthyridinyl group optionally substituted with X and Y,

r)  ,

s)  ,

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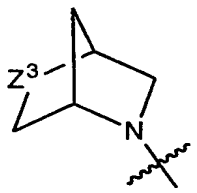
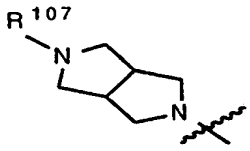
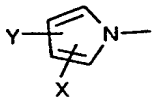
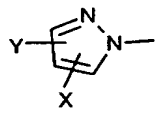
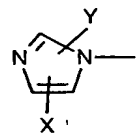
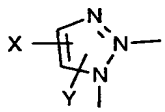
t)  ,

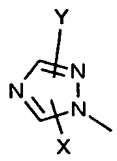
u)  ,

v)  ,

w)  ,

x)  ,

y)  ,

z)  ,

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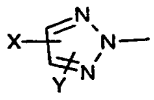
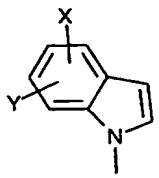
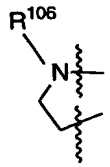
aa)  ,

bb)  or

Q and R_{24} taken together are

 ,

wherein Z^1 is

a) $-CH_2-$,

b) $-CH(R^{104})-CH_2-$,

c) -C(O)-, or

d) $-CH_2CH_2CH_2-$;

wherein Z^2 is

a) $-O_2S-$,

b) -O-,

c) $-N(R^{107})-$,

d) -OS-, or

e) -S-;

wherein Z^3 is

a) $-O_2S-$,

b) -O-,

c) -OS-, or

d) -S-;

wherein A^1 is

a) H-, or

b) CH_3;

wherein A^2 is

a) H-,

b) HO-,

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c) CH_3-,

d) CH_3O-,

e) $R^{102}O$-CH_2-C(O)-NH-

f) $R^{103}O$-C(O)-NH-,

g) (C_1-C_2)alkyl-O-C(O)-,

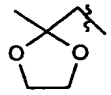
h) HO-CH_2-,

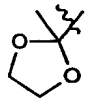
i) CH_3O-NH-,

j) (C_1-C_3)alkyl-O_2C-

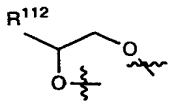
k) CH_3-C(O)-,

l) CH_3-C(O)-CH_2-,

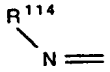
m)  , or

n)  ,

A^1 and A^2 taken together are:

a)  ,

b) O= , or

c)  ;

wherein R^{102} is

a) H-,

b) CH_3-,

c) phenyl-CH_2-, or

d) $CH_3C(O)$-;

wherein R^{103} is

a) (C_1-C_3)alkyl-, or

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b) phenyl-;

wherein R^{104} is

a) H-, or

b) HO-;

wherein R^{105} is

a) H-,

b) $(C_1\text{-}C_3)$alkyl-,

c) $CH_2 = CH\text{-}CH_2$-, or

d) $CH_3\text{-}O\text{-}(CH_2)_2$-;

wherein R^{106} is

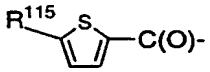
a) $CH_3\text{-}C(O)$-,

b) H-C(O)-,

c) $Cl_2CH\text{-}C(O)$-,

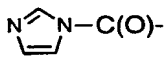
d) $HOCH_2\text{-}C(O)$-,

e) CH_3SO_2-,

f) 

,

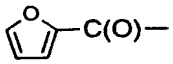
g) $F_2CHC(O)$-,

h) 

,

i) $H_3C\text{-}C(O)\text{-}O\text{-}CH_2\text{-}C(O)$-,

j) $H\text{-}C(O)\text{-}O\text{-}CH_2\text{-}C(O)$-,

k) 

,

l) $HC{\equiv}C\text{-}CH_2O\text{-}CH_2\text{-}C(O)$-, or

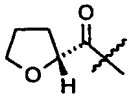
m) phenyl-$CH_2\text{-}O\text{-}CH_2\text{-}C(O)$-;

wherein R^{107} is

a) $R^{102}O\text{-}C(R^{110})(R^{111})\text{-}C(O)$-,

b) $R^{103}O\text{-}C(O)$-,

c) $R^{108}\text{-}C(O)$-,

d) 

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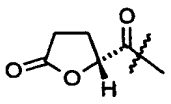
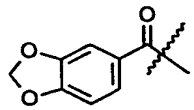
e)  ,

f) H_3C-C(O)-$(CH_2)_2$-C(O)-,

g) R^{109}-SO_2-,

h)  ,

i) HO-CH_2-C(O)-,

j) R^{116}-$(CH_2)_2$-,

k) R^{113}-C(O)-O-CH_2-C(O)-,

l) $(CH_3)_2$N-CH_2-C(O)-NH-,

m) NC-CH_2-, or

n) F_2-CH-CH_2-;

wherein R^{108} is

a) H-,

b) $(C_1$-$C_4)$alkyl,

c) aryl -$(CH_2)_p$,

d) ClH_2C-,

e) Cl_2HC-,

f) FH_2C-,

g) F_2HC-, or

h) $(C_3$-$C_6)$cycloalkyl;

wherein R^{109} is

a) -CH_3,

b) -CH_2Cl

c) -$CH_2CH{=}CH_2$,

d) aryl, or

e) -CH_2CN;

wherein R^{110} and R^{111} are independently

a) H-,

b) CH_3-; or

wherein R^{112} is

a) H-,

b) CH_3O-CH_2O-CH_2-, or

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c) $HOCH_2$-;

wherein R^{113} is

a) CH_3-,

b) $HOCH_2$-,

c) $(CH_3)_2N$-phenyl, or

d) $(CH_3)_2N$-CH_2-;

wherein R^{114} is

a) HO-,

b) CH_3O-,

c) H_2N-,

d) CH_3O-C(O)-O-,

e) CH_3-C(O)-O-CH_2-C(O)-O-,

f) phenyl-CH_2-O-CH_2-C(O)-O-,

g) HO-$(CH_2)_2$-O-,

h) CH_3O-CH_2-O-$(CH_2)_2$-O-, or

i) CH_3O-CH_2-O-;wherein R^{113} is

a) CH_3-,

b) $HOCH_2$-,

c) $(CH_3)_2N$-phenyl, or

d) $(CH_3)_2N$-CH_2-;

wherein R^{115} is

a) H-, or

b) Cl-;

wherein R^{116} is

a) HO-

b) CH_3O-, or

c) F;

B is an unsaturated 4-atom linker having one nitrogen and three carbons;

M is

a) H,

b) C_{1-8} alkyl,

c) C_{3-8} cycloalkyl,

d) $-(CH_2)_mOR_{13}$, or

e) $-(CH_2)_h-NR_{21}R_{22}$;

Z is

a) O,

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b) S, or

c) NM;

W is

a) CH,

b) N, or

c) S or O when Z is NM;

Y is

a) H,

b) F,

c) Cl,

d) Br,

e) C_{1-3} alkyl, or

f) NO_2;

X is

a) H,

b) -CN,

c) OR_{27},

d) halo,

e) NO_2,

f) tetrazoyl,

g) -SH,

h) $-S(=O)_iR_4$,

i) $-S(=O)_2-N=S(O)_jR_5R_6$,

j) $-SC(=O)R_7$,

k) $-C(=O)R_{25}$,

l) $-C(=O)NR_{27}R_{28}$,

m) $-C(=NR_{29})R_{25}$,

n) $-C(R_{25})(R_{28})-OR_{13}$,

o) $-C(R_{25})(R_{28})-OC(=O)R_{13}$,

p) $-C(R_{28})(OR_{13})-(CH_2)_h-NR_{27}R_{28}$,

q) $-NR_{27}R_{28}$,

r) $-N(R_{27})C(=O)R_7$,

s) $-N(R_{27})-S(=O)_iR_7$,

t) $-C(OR_{14})(OR_{15})R_{28}$,

u) $-C(R_{25})(R_{16})-NR_{27}R_{26}$, or

v) C_{1-8} alkyl substituted with one or more halos, OH, =O other than at

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alpha position, $-S(=O)_iR_{17}$, $-NR_{27}R_{28}$, C_{2-5} alkenyl, C_{2-5} alkynyl, or C_{3-8} cycloalkyl;

R_4, R_5, R_6, R_7, R_{13}, R_{14}, R_{15}, R_{16}, and R_{17} are the same as defined above;

R_{25} is

a) H,

b) C_{1-8} alkyl optionally substituted with one or more halos, C_{3-8} cycloalkyl, C_{1-4} alkyl substituted with one or more of $-S(=O)_iR_{17}$, $-OR_{13}$, or $OC(=O)R_{13}$, $NR_{27}R_{28}$, or

c) C_{2-5} alkenyl optionally substituted with CHO, or CO_2R_{13};

R_{26} is

a) R_{28}, or

b) $NR_{27}N_{28}$;

R_{27} and R_{28} at each occurrence are the same or different and are

a) H,

b) C_{1-8} alkyl,

c) C_{3-8} cycloalkyl,

d) $-(CH_2)_mOR_{13}$,

e) $-(CH_2)_h-NR_{21}R_{22}$, or

f) R_{27} and R_{28} taken together are $-(CH_2)_2O(CH_2)_2-$, $-(CH_2)_hCH(COR_7)-$, or $-(CH_2)_2N(CH_2)_2(R_7)$;

R_{29} is

a) $-NR_{27}R_{28}$,

b) $-OR_{27}$, or

c) $-NHC(=O)R_{28}$;

wherein R_{30} is

a) H,

b) C_{1-8} alkyl optionally substituted with one or more halos, or

c) C_{1-8} alkyl optionally substituted with one or more OH, or C_{1-6} alkoxy;

wherein E is

a) NR_{39},

b) $-S(=O)_i$, or

c) O;

R_{38} is

a) H,

b) C_{1-6} alkyl,

c) $-(CH_2)_q$-aryl, or

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d) halo;

R_{39} is

a) H,

b) C_{1-6} alkyl optionally substituted with one or more OH, halo, or -CN,

c) $-(CH_2)_q$-aryl,

d) $-CO_2R_{40}$,

e) $-COR_{41}$,

f) $-C(=O)-(CH_2)_q-C(=O)R_{40}$,

g) $-S(=O)_2-C_{1-6}$ alkyl,

h) $-S(=O)_2-(CH_2)_q$-aryl, or

i) $-(C=O)_j$-Het;

R_{40} is

a) H,

b) C_{1-6} alkyl optionally substituted with one or more OH, halo, or -CN,

c) $-(CH_2)_q$-aryl, or

d) $-(CH_2)_q-OR_{42}$;

R_{41} is

a) C_{1-6} alkyl optionally substituted with one or more OH, halo, or -CN,

b) $-(CH_2)_q$-aryl, or

c) $-(CH_2)_q-OR_{42}$;

R_{42} is

a) H,

b) C_{1-6} alkyl,

c) $-(CH_2)_q$-aryl, or

d) $-C(=O)-C_{1-6}$ alkyl;

aryl is

a) phenyl,

b) pyridyl, or

c) napthyl; a to c optionally substituted with one or more halo, -CN, OH, SH, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} alkylthio;

wherein R_{43} is

a) H,

b) C_{1-2} alkyl,

c) F, or

d) OH;

R_{44} is

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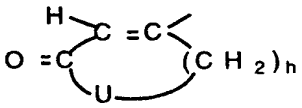
a) H,

b) CF_3,

c) C_{1-3} alkyl optionally substituted with one or more halo,

d) phenyl optionally substituted with one or more halo,

e) R_{44} and R_{45} taken together are a 5-, 6-, or 7-membered ring of the formula,

or 

f) R_{44} and R_{45} taken together are $-(CH_2)_k-$, when R_{46} is an electron-withdrawing group;

R_{45} and R_{46} at each occurrence are the same or different and are

a) an electron-withdrawing group,

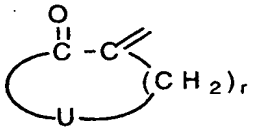
b) H,

c) CF_3,

d) C_{1-3} alkyl optionally substituted with one halo,

e) phenyl, provided at least one of R_{45} or R_{46} is an electron-withdrawing group, or

f) R_{45} and R_{46} taken together are a 5-, 6-, 7-membered ring of the formula



;

U is

a) CH_2,

b) O,

c) S, or

d) NR_{47};

R_{47} is

a) H, or

b) C_{1-5} alkyl;

wherein R_{48} is

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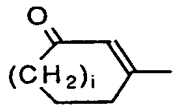
a) carboxyl,
b) halo,
c) -CN,
d) mercapto,
e) formyl,
f) CF_3,
g) $-NO_2$,
h) C_{1-6} alkoxy,
i) C_{1-6} alkoxycarbonyl,
j) C_{1-6} alkythio,
k) C_{1-6} acyl,
l) $-NR_{49}R_{50}$,
m) C_{1-6} alkyl optionally substituted with OH, C_{1-5} alkoxy, C_{1-5} acyl, or $-NR_{49}R_{50}$,
n) C_{2-8} alkenylphenyl optionally substituted with one or two R_{51},
o) phenyl optionally substituted with one or two R_{51},
p) a 5-, or 6-membered (un)saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with one or two R_{51}, or
q) 

;

R_{49} and R_{50} at each occurrence are the same or different and are
a) H,
b) C_{1-4} alkyl,
c) C_{5-6} cycloalkyl, or
d) R_{49} and R_{50} taken together with the nitrogen atom is a 5-, 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, and O, and can in turn be optionally substituted with, including on the further nitrogen atom, C_{1-3} alkyl, or C_{1-3} acyl;

R_{51} is
a) carboxyl,
b) halo,
c) -CN,
d) mercapto,

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e) formyl,
f) CF_3,
g) $-NO_2$,
h) C_{1-6} alkoxy,
i) C_{1-6} alkoxycarbonyl,
j) C_{1-6} alkythio,
k) C_{1-6} acyl,
l) C_{1-6} alkyl optionally substituted with OH, C_{1-5} alkoxy, C_{1-5} acyl, or $-NR_{49}R_{50}$,
m) phenyl,
n) $-C(=O)NR_{52}\ R_{53}$,
o) $-NR_{49}R_{50}$,
p) $-N(R_{52})(-SO_2R_{54})$,
q) $-SO_2-NR_{52}R_{53}$, or
r) $-S(=O)_iR_{54}$;

R_{52} and R_{53} at each occurrence are the same or different and are
a) H,
b) C_{1-6} alkyl, or
c) phenyl;

R_{54} is
a) C_{1-4} alkyl, or
b) phenyl optionally substituted with C_{1-4} alkyl;

wherein R_{55} is
a) carboxyl,
b) halo,
c) -CN,
d) mercapto,
e) formyl,
f) CF_3,
g) $-NO_2$,
h) C_{1-6} alkoxy,
i) C_{1-6} alkoxycarbonyl,
j) C_{1-6} alkythio
k) C_{1-6} acyl,
l) $-NR_{56}\ R_{57}$,
m) C_{1-6} alkyl optionally substituted with OH, C_{1-5} alkoxy, C_{1-5} acyl, or

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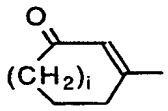
$-NR_{56}R_{57}$,

n) C_{2-8} alkenylphenyl optionally substituted with one or two R_{58},

o) phenyl optionally substituted with one or two R_{58},

p) a 5- or 6-membered (un)saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with one or two R_{58}, or

q)  ;

R_{56} and R_{57} at each occurrence are the same or different and are

a) H,

b) formyl,

c) C_{1-4} alkyl,

d) C_{1-4} acyl,

e) phenyl,

f) C_{3-6} cycloalkyl, or

g) R_{56} and R_{57} taken together with the nitrogen atom is a 5-, 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, and O, and can in turn be optionally substituted with, including on the further nitrogen atom, phenyl, pyrimidyl, C_{1-3} alkyl, or C_{1-3} acyl;

R_{58} is

a) carboxyl,

b) halo,

c) -CN,

d) mercapto,

e) formyl,

f) CF_3,

g) $-NO_2$,

h) C_{1-6} alkoxy,

i) C_{1-6} alkoxycarbonyl,

j) C_{1-6} alkythio,

k) C_{1-6} acyl,

l) phenyl,

m) C_{1-6} alkyl optionally substituted with OH, azido, C_{1-5} alkoxy, C_{1-5} acyl,

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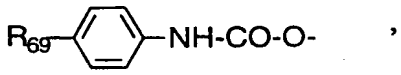
$-NR_{65}R_{66}$, $-SR_{67}$, $-O-SO_2R_{68}$, or



n) $-C(=O)NR_{59}\ R_{60}$,

o) $-NR_{56}R_{57}$,

p) $-N(R_{59})(-SO_2R_{54})$,

q) $-SO_2-NR_{59}R_{60}$,

r) $-S(=O)_iR_{54}$,

s) $-CH=N-R_{61}$, or

t) $-CH(OH)-SO_3R_{64}$;

R_{54} is the same as defined above;

R_{59} and R_{60} at each occurrence are the same or different and are

a) H,

b) C_{1-6} alkyl,

c) phenyl, or

d) tolyl;

R_{61} is

a) OH,

b) benzyloxy,

c) $-NH-C(=O)-NH_2$,

d) $-NH-C(=S)-NH_2$, or

e) $-NH-C(=NH)-NR_{62}R_{63}$;

R_{62} and R_{63} at each occurrence are the same or different and are

a) H, or

b) C_{1-4} alkyl optionally substituted with phenyl or pyridyl;

R_{64} is

a) H, or

b) a sodium ion;

R_{65} and R_{66} at each occurrence are the same or different and are

a) H,

b) formyl,

c) C_{1-4} alkyl,

d) C_{1-4} acyl,

e) phenyl,

f) C_{3-6} cycloalkyl,

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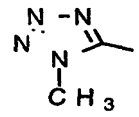
g) R_{65} and R_{66} taken together are a 5-, 6-membered saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with, including on the nitrogen atom, phenyl, pyrimidyl, C_{1-3} alkyl, or C_{1-3} acyl,

h) $-P(O)(OR_{70})(OR_{71})$, or

i) $-SO_2-R_{72}$;

R_{67} is



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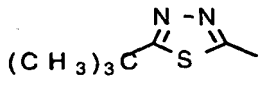

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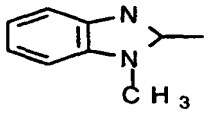
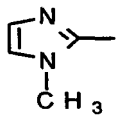


, or


;

R_{68} is C_{1-3} alkyl;

R_{69} is

a) C_{1-6} alkoxycarbonyl, or

b) carboxyl;

R_{70} and R_{71} at each occurrence are the same or different and are

a) H, or

b) C_{1-3} alkyl;

R_{72} is

a) methyl,

b) phenyl, or

c) tolyl;

wherein K is

a) O, or

b) S;

R_{73}, R_{74}, R_{75}, R_{76}, and R_{77} at each occurrence are the same or different and are

a) H,

b) carboxyl,

c) halo,

d) -CN,

e) mercapto,

f) formyl,

g) CF_3,

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h) $-NO_2$,

i) C_{1-6} alkoxy,

j) C_{1-6} alkoxycarbonyl,

k) C_{1-6} alkythio,

l) C_{1-6} acyl,

m) $-NR_{78}R_{79}$,

n) C_{1-6} alkyl optionally substituted with OH, C_{1-5} alkoxy, C_{1-5} acyl, $-NR_{78}R_{79}$, -N(phenyl)(CH_2-CH_2-OH), -O-CH(CH_3)(OCH_2CH_3), or -O-phenyl-[para-NHC(=O)CH_3],

o) C_{2-8} alkenylphenyl optionally substituted with R_{51},

p) phenyl optionally substituted with R_{51}, or

q) a 5-, or 6-membered (un)saturated heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, optionally substituted with R_{51};

R_{51} is the same as defined above;

R_{78} and R_{79} at each occurrence are the same or different and are

a) H,

b) C_{1-4} alkyl,

c) phenyl, or

d) R_{78} and R_{79} taken together with the nitrogen atom is a 5-, 6-membered saturated heterocyclic moiety which optionally has a further hetero atom selected from the group consisting of S, N, and O, and can in turn be optionally substituted with, including on the further nitrogen atom, C_{1-3} alkyl, or C_{1-3} acyl;

wherein T is

a) O,

b) S, or

c) SO_2;

R_{75}, R_{76}, and R_{77} are the same as defined above;

R_{80} is

a) H,

b) formyl,

c) carboxyl,

d) C_{1-6} alkoxycarbonyl,

e) C_{1-8} alkyl,

f) C_{2-8} alkenyl,

wherein the substituents (e) and (f) can be optionally substituted with OH, halo, C_{1-6} alkoxy, C_{1-6} acyl, C_{1-6} alkylthio or C_{1-6} alkoxycarbonyl, or phenyl optionally substituted with halo,

g) an aromatic moiety having 6 to 10 carbon atoms optionally substituted with carboxyl, halo, -CN, formyl, CF_3, $-NO_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} acyl, C_{1-6} alkylthio, or C_{1-6} alkoxycarbonyl;

h) $-NR_{81}R_{82}$,

i) $-OR_{90}$,

j) $-S(=O)_i-R_{91}$,

k) $-SO_2-N(R_{92})(R_{93})$, or

l) a radical of the following formulas:

R_{81} and R_{82} at each occurrence are the same or different and are

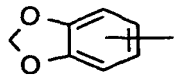
a) H,

b) C_{3-6} cycloalkyl,

c) phenyl,

d) C_{1-6} acyl,

e) C_{1-8} alkyl optionally substituted with OH, C_{1-6} alkoxy which can be substituted with OH, a 5-, or 6-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O, phenyl optionally substituted with OH, CF_3, halo, $-NO_2$, C_{1-4} alkoxy, $-NR_{83}R_{84}$, or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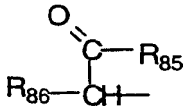
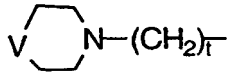
f)

, or

g)

;

V is

a) O,

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b) CH_2, or

c) NR_{87};

R_{83} and R_{84} at each occurrence are the same or different and are

a) H, or

b) C_{1-4} alkyl;

R_{85} is

a) OH,

b) C_{1-4} alkoxy, or

c) $-NR_{88}R_{89}$;

R_{86} is

a) H, or

b) C_{1-7} alkyl optionally substituted with indolyl, OH, mercaptyl, imidazoly, methylthio, amino, phenyl optionally substituted with OH, $-C(=O)-NH_2$, $-CO_2H$, or $-C(=NH)-NH_2$;

R_{87} is

a) H,

b) phenyl, or

c) C_{1-6} alkyl optionally substituted by OH;

R_{88} and R_{89} at each occurrence are the same or different and are

a) H,

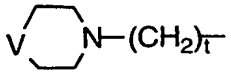
b) C_{1-5} alkyl

c) C_{3-6} cycloalky, or

d) phenyl;

R_{90} is

a) C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy or C_{1-6} hydroxy, C_{3-6} cycloalkyl, a 6-membered aromatic optionally benzo-fused heterocyclic moiety having one to three nitrogen atoms, which can in turn be substituted with one or two $-NO_2$, CF_3, halo, -CN, OH, C_{1-5} alkyl, C_{1-5} alkoxy, or C_{1-5} acyl;

b)  ,

c) phenyl, or

d) pyridyl;

R_{91} is

a) C_{1-16} alkyl,

b) C_{2-16} alkenyl,

wherein the substituents (a) and (b) can be optionally substituted with C_{1-6} alkoxycarbonyl, or a 5-, 6-, 7-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,

c) an aromatic moiety having 6 to 10 carbon atoms, or

d) a 5-, 6-, 7-membered aromatic heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,

wherein the substituents (c) and (d) can be optionally substituted with carboxyl, halo, -CN, formyl, CF_3, $-NO_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} acyl, C_{1-6} alkylthio, or C_{1-6} alkoxycarbonyl;

R_{92} and R_{93} at each occurrence are the same or different and are

a) H,

b) phenyl,

c) C_{1-6} alkyl, or

d) benzyl;

R_{94} and R_{95} at each occurrence are the same or different and are

a) H,

b) OH,

c) C_{1-6} alkyl optionally substituted with $-NR_{83}R_{84}$, or

d) R_{94} and R_{95} taken together are =O;

R_{96} is

a) an aromatic moiety having 6 to 10 carbon atoms,

b) a 5-, or 6-membered aromatic optionally benzo-fused heterocyclic moiety having one to three atoms selected from the group consisting of S, N, and O,

wherein the substituents (a) and (b) which can in turn be substituted with one or three $-NO_2$, CF_3, halo, -CN, OH, phenyl, C_{1-5} alkyl, C_{1-5} alkoxy, or C_{1-5} acyl,

c) morpholinyl,

d) OH,

e) C_{1-6} alkoxy,

f) $-NR_{83}R_{84}$,

g) $-C(=O)-R_{97}$, or

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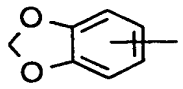
h)  ;

R_{97} is

a) morpholinyl,

b) OH, or

c) C_{1-6} alkoxy;

h is 1, 2, or 3;

i is 0, 1, or 2;

j is 0 or 1;

k is 3, 4, or 5;

l is 2 or 3;

m is 4 or 5;

n is 0, 1, 2, 3, 4, or 5;

p is 0, 1, 2, 3, 4, or 5; with the proviso that n and p together are 1, 2, 3, 4, or 5;

q is 1, 2, 3, or 4;

r is 2, 3, or 4;

t is 0, 1, 2, 3, 4, 5, or 6;

u is 1 or 2.

2. A compound of Claim 1 which is :

a) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;

b) (S)-N-[[3-[3-Fluoro-4-[4-(5-methyl-1,3,4-thiadiazol-2-yl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;

c) (S)-N-[[3-[3-Fluoro-4-[2′,5′-dioxospiro[piperidine-4,4′-imidazolidine]-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;

d) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;

e) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea;

f) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-N′-methylthiourea;

g) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-thioformamide;

h) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-

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oxazolidinyl]methyl]thiopropion-amide;

i) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-2-chlorothioacetamide;

j) (S)-N-[[3-[3-Fluoro-4-(4-moropholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α,α,α-trifluorothioacetamide;

k) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α-fluorothioacetamide;

l) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α,α-difluorothioacetamide;

m) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α-cyanothioacetamide;

n) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α,α-dichlorothioacetamide;

o) (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-α-(methoxycarbonyl)thioacetamide;

p) (S)-N-[[3-[4-[1-[1,2,4]Triazolyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;

q) (S)-N-[[3-[4-[1-[1,2,4]Triazolyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;

r)) (S)-N-[[3-[1-(Hydroxyacetyl)-5-indolinyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;

s) (S)-N-[[3-[3-Fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;

t) (S)-N-[[3-[3-Fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thio-acetamide;

u) (S)-N-[[3-[3-Fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thio-acetamide, thiomorpholine S-oxide;

v) (S)-N-[[3-[3-Fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thio-acetamide, thiomorpholine S, S-dioxide;

w) (S)-N-[[3-[3,5-Difluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide;

x) (S)-N-[[3-[4-[1-[1,2,4]Triazolyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]thiourea;

y) (*S*)-N-[[3-[3-Fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]-methyl]thiourea;

z) (S)-N-[[3-[1-(Hydroxyacetyl)-5-indolinyl]-2-oxo-5-

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oxazolidinyl]methyl]thiourea;

aa) (S)-N-[[3-[3-Fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methylthiourea, thiomorpholine S-oxide;

bb) (*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl-S-methyldithiocarbamate;

3. A method for treating microbial infections in patients comprising administering to a patient in need thereof an effective amount of a compound of Formula I.

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INTERNATIONAL SEARCH REPORT

.n\ .tional Application No
PCT/US 98/09889

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D263/20 C07D417/12 C07D413/10 C07D413/04 A61K31/42 C07D261/04 C07D307/32 C07D471/10 //(C07D471/10,235:00, 221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 127 902 A (E.I.DU PONT DE NEMOURS AND COMPANY) 12 December 1984 see claims ---	1-3
Y	EP 0 184 170 A (E.I. DU PONT DE NEMOURS AND COMPANY) 11 June 1986 see claims ---	1-3
Y	EP 0 359 418 A (THE UPJOHN COMPANY) 21 March 1990 see claims ---	1-3
Y	WO 95 07271 A (THE UPJOHN COMPANY) 16 March 1995 see claims ---	1-3
Y	WO 97 14690 A (ZENECA LTD) 24 April 1997 see claims --- -/--	1-3

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 August 1998	21/08/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Henry, J

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Form PCT/ISA/210 (second sheet) (July 1992)

RNSDOCID: <WO 9854161A1 IA>

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/09889

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,Y	EP 0 789 025 A (BAYER AG) 13 August 1997 see page 33 - page 41; claims	1-3
P,Y	WO 98 07708 A (PHARMACIA & UPJOHN COMPANY) 26 February 1998 see claims	1-3
P,Y	DE 196 01 264 A (BAYER AG) 17 July 1997 see page 20 - page 23; claims	1-3

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

BNSDOCID: <WO 9854161A1 IA>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/ 09889

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 3
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 3 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: not applicable
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: not applicable

In view of the extremely broad Markush claims, the search was executed with due regard to the PCT Search Guidelines (PCT/GL/2), C-III, paragraph 2.1, 2.3 read in conjunction with 3.7 and Rule 33.3 PCT, i.e. particular emphasis was put on the inventive concept, as illustrated by the examples and the compounds of claim 2.
The international search was, in so far as possible and reasonable, complete in that it covered the entire subject-matter to which the claims are directed.

RNSDOCID: <WO 9854161A1 IA>

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/09889

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0127902 A	12-12-1984	AU 583250 B	27-04-1989
		AU 2909984 A	13-12-1984
		CA 1254213 A	16-05-1989
		CA 1275652 A	30-10-1990
		DE 3485162 A	21-11-1991
		DK 279584 A	08-12-1984
		FI 842273 A,B	08-12-1984
		JP 60008277 A	17-01-1985
		MX 169619 B	15-07-1993
		SU 1505442 A	30-08-1989
		SU 1426451 A	23-09-1988
		US 4705799 A	10-11-1987
EP 0184170 A	11-06-1986	AU 611627 B	20-06-1991
		AU 5081685 A	11-06-1987
		CA 1260948 A	26-09-1989
		DE 3584427 A	21-11-1991
		DK 561885 A	06-06-1986
		FI 854804 A,B	06-06-1986
		IE 58325 B	08-09-1993
		JP 61134379 A	21-06-1986
		PT 81610 B	21-04-1988
		SU 1528317 A	07-12-1989
		US 4705799 A	10-11-1987
EP 0359418 A	21-03-1990	AT 112773 T	15-10-1994
		AU 617871 B	05-12-1991
		AU 4195789 A	02-04-1990
		CA 1335103 A	04-04-1995
		DE 68918792 D	17-11-1994
		DK 45591 A	13-03-1991
		EP 0434714 A	03-07-1991
		EP 0609905 A	10-08-1994
		JP 4500665 T	06-02-1992
		WO 9002744 A	22-03-1990
		US 5164510 A	17-11-1992
		US 5182403 A	26-01-1993
		US 5225565 A	06-07-1993
WO 9507271 A	16-03-1995	AU 687866 B	05-03-1998

BNSDOCID: <WO 9854161A1_IA>

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/09889

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9507271 A		AU 7557094 A	27-03-1995
		CA 2168560 A	16-03-1995
		CN 1130379 A	04-09-1996
		EP 0717738 A	26-06-1996
		JP 9502436 T	11-03-1997
		ZA 9405894 A	05-02-1996
WO 9714690 A	24-04-1997	AU 7224896 A	07-05-1997
EP 0789025 A	13-08-1997	DE 19604223 A	07-08-1997
		AU 1251697 A	14-08-1997
		CA 2196862 A	07-08-1997
		CN 1160051 A	24-09-1997
		CZ 9700340 A	13-08-1997
		HR 970048 A	30-04-1998
		JP 9316073 A	09-12-1997
		NO 970511 A	07-08-1997
		PL 318277 A	18-08-1997
		SK 15897 A	08-10-1997
WO 9807708 A	26-02-1998	AU 3973697 A	06-03-1998
DE 19601264 A	17-07-1997	AU 1009897 A	24-07-1997
		CA 2194938 A	17-07-1997
		CZ 9700129 A	13-08-1997
		EP 0785200 A	23-07-1997
		HR 960615 A	28-02-1998
		JP 9194482 A	29-07-1997
		NO 970175 A	17-07-1997
		PL 317929 A	21-07-1997
		SK 5997 A	10-09-1997

BNSDOCID: <WO _9854161A1_IA>